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Neonate with 10q Interstitial Deletion within the Long Arm of Chromosome 10- A Case Report and Literature Review

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ABSTRACT

Introduction: Partial deletion of distal chromosome 10q was first reported in 1978 by Lewandowski[1]. Interstitial deletions within bands 10q25e10q26.3 are rare. Seven such cases were reported so far[2]. **Patient Information:** A term AGA male newborn was delivered at our perinatal center with antenatal diagnosis of unbalanced translocation of chromosomes 10 and 12, and fetal cleft lip and cleft palate. Blood was sent for chromosome analysis using GTG banding method. Baby had facial dysmorphism, left cleft lip, bilateral cleft of soft and hard palate, intact nasal septum, normal ears and micrognathus. Abdominal ultrasound showed absence of right testis in inguinal canal and abdomen (anorchia). Hospital course was unremarkable except for feeding problems requiring feeding team, plastic surgery planned at 2- 3 months of age, and taping of the cleft lip. He went home on day 7. **Conclusion**: Here, we reported an extremely rare case of a male newborn with an interstitial deletion within the long arm of chromosome 10 between bands 10q25.1 and 10q26.1, with dysmorphic features, along with a few unreported associations (atypical Pierre-Robin sequence and bilateral dorsal horn ventriculomegaly). We added a comprehensive review of literature on chromosome 10q deletions to the case report. We also listed clinical implications of 71 RefSeq and OMIM genes noted in that ~13.3Mb 10q deletion in the Appendix. Earlier detection of both common and rare chromosomal- genetic abnormalities might prepare the family and health care team to plan optimal care to the mother, and baby.

Keywords: Chromosome 10 q deletions, Interstitial deletions, Cleft lip and Cleft palate anomalies

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INTRODUCTION

In 1978 Lewandowski et al[1], described the first case of partial deletion of the long arm of 10 chromosome (10q). Since then, there have been more than 110 reported cases[3] involving terminal deletions on the chromosome 10q. The possibility of a distinct distal 10q deletion syndrome (Online Mendelian Inheritance in Man- OMIM 609625)[4] was proposed by Wulfsberg et al in 1989 [5], and was further endorsed by others including Irving[6] et al in 2003. It has been noted that most terminal deletions had breakpoints in bands 10q25 or 10q26. Also, it has been observed that 10q deletions tend to have heterogeneous clinical presentations. Commonly reported clinical features include growth restriction (intra-uterine and/or extra-uterine), dysmorphic facial features, cranial asymmetry, sensorineural hearing loss, vestibular dysfunction, skeletal anomalies, varying degrees of neurodevelopmental delays especially in cognitive and motor areas, cardiovascular, ano-genital and genito-urinary anomalies [2, to 13].

Among the Chromosome 10q deletion disorders, interstitial deletions are exceedingly rare. Those, interstitial deletions specifically within bands 10q25e10q26.3 are exceptional. About 7 such cases of 10q interstitial deletions have been reported [2].

Here, we are reporting another very exceptional case of a term male newborn, with a proven interstitial deletion within the chromosome 10q between bands 10q25.1 and 10q26.1, associated with dysmorphic features, right anorchia, and unreported associations such as atypical Pierre-Robin sequence (micrognathia, bilateral cleft palate (not reverse “U” shaped), and glossoptosis), cleft lip, and bilateral dorsal horn ventriculomegaly. Referral by an attentive primary Obstetrician from a nearby town, to our perinatal center for the evaluation of antenatal cleft lip and cleft palate, and the diligence exercised by our maternal fetal medicine specialist, helped us to suspect a genetic condition, prenatally. Unbalanced translocation of chromosome 10 and 12 was suspected during the antenatal evaluation, prior to making the final diagnosis using GTG banding (Giemsa banding), on the infant’s blood.

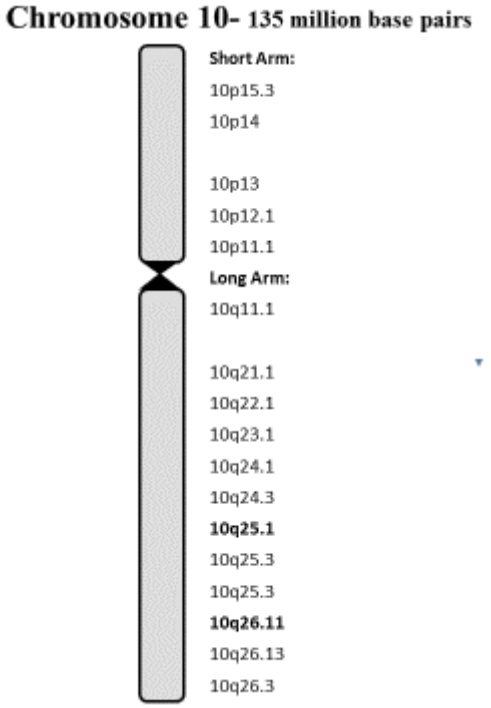
Clinical information was obtained from a retrospective chart review. A case report was prepared following the CARE guidelines [14]. We did an extensive literature search on Chromosome 10 q- deletions, using PubMed, OVID Medline and Scopus data bases. A comprehensive review of the medical literature on both terminal and interstitial deletions of 10q is presented.

PATIENT INFORMATION

A term male newborn was delivered by spontaneous vaginal delivery under epidural anesthesia at our level IV perinatal center. Mother was a 32 year old gravida 3, para 2 Caucasian female with no prior medical problems. Pregnancy history was negative for any other medical issues including gestational diabetes, pre-eclampsia, thyroid disorders, epilepsy, neurological disorders, and substance abuse including tobacco, alcohol, or recreational drugs. There was no reported consanguinity of the parents. Paternal history was also negative for substance abuse, and other medical disorders. Family history on paternal and maternal sides was negative for cleft lip, cleft palate, dysmorphic features, hearing loss, vision problems (no signs suggestive of Stickler syndrome), thyroid disorders, growth disorders, intellectual deficits, neuro-development disorders, chromosomal or genetic abnormalities, skeletal, cardiac, and renal abnormalities during childhood. Antenatal diagnoses of suspected unbalanced translocation of chromosomes 10 and 12, with fetal cleft lip and cleft palate were made at our perinatal center.

He had Apgar scores of 8 and 9 at 1 minute and 5 minutes of age, and had a birth weight of 3.5 kilograms (58th%ile), length of 49.5 cm (37th%ile), and head circumference of 35 cm (57th%ile). All growth parameters were appropriate for gestational age (AGA). The baby

had dysmorphic features that included sloping frontal region, normal anterior fontanel, hypertelorism, flattened nasal bridge, cleft lip on the left with cleft of soft and hard palate, cleft of the soft and hard palate on the right without cleft lip (atypical Pierre-Robin sequence), intact nasal septum, normal ears and micrognathus. Other relevant findings included normal shaped chest, appropriately spaced nipples, no heart murmur, 3 vessel cord, no abdominal organomegaly, right cryptorchidism, patent anus and base visible sacral dimple. Hospital course was remarkable for feeding problems requiring feeding team, and plastic surgery consult requiring taping of the cleft lip with plans for surgery at 2- 3 months of age. Patient was discharged home on day 7. Parents declined to be tested.



DIAGNOSTIC ASSESSMENT

The following investigations and consultations were obtained during the infant's hospital stay: a) an echocardiogram done on day 2 showed trivial tricuspid regurgitation (TR) and no structural heart defect, b) brain MRI done on day 3, revealed dilated dorsal horns of lateral ventricles with decompressed 3rd and 4th ventricles and prominent perivascular spaces, c) passed hearing screening (both ears), d) abdominal ultrasound showed absence of right testis in inguinal canal and abdomen (anorchia), e) TSH and T4 were normal; blood glucose screens were all normal, f) genetic, plastic surgery, and speech therapy consultations were obtained, g) cytogenetic analysis- using standard procedures, routine GTG banding (Giemsa banding) was performed on peripheral blood specimen of the baby (a technique used in cytogenetics to produce visible karyotype by staining condensed chromosomes), h) Chromosomal analysis revealed an abnormal male chromosome complement in all cells examined with an interstitial deletion within the long arm of chromosome 10, between bands 10q25.1 and 10q26.1 (46, XY, del(10)(q25.1q26.1). Gene mapping results showed a number of genes in the region of deletion. The size of the interstitial deletion is ~13.3Mb encompassing 71 RefSeq and OMIM genes (Refer to the image of the chromosome 10, and the supplement- appendix for the list of genes in this deleted segment).

DISCUSSION

We are reporting an exceedingly rare case of a term male newborn with an interstitial deletion within the long arm of chromosome 10, between bands 10q25.1 and 10q26.1 (size ~13,3 Mb), and with a few new associations. Among the three types of deletions (terminal, intercalary/interstitial, and microdeletion) within the long arm of chromosome 10, interstitial deletions are very rare. Among them, interstitial deletions specifically within bands 10q25e10q26.3 are extremely infrequent (about 7 reported cases in English literature) [2].

Since Lewandowski's first report in 1978, there have been reports of various combinations of dysmorphic and clinical features that covered mostly terminal 10q deletion syndrome. During the neonatal period, infancy, and toddler age, reported features included Intra- uterine growth restriction (IUGR), extra- uterine growth restriction (EUGR), cranial asymmetry, microcephaly, craniosynostosis, hypertelorism, strabismus, coloboma, cataract, thin upper lip, prominent nose and nasal bridge, prominent (dysplastic) ears, sensorineural hearing loss, vestibular dysfunction, cystichygroma, skeletal anomalies (digital and limb abnormalities), cardiovascular (congenital heart disease- PDA, VSD, ASD; left ventricular enlargement), urinary tract anomalies (mega-bladder), anogenital and genitourinary anomalies (cryptorchidism, micropenis, sex reversal or ambiguous genitalia), varying degrees of neurodevelopmental delays, especially in cognitive and motor areas, learning disabilities, feeding difficulties, hypotonia, autism spectrum, and behavior problems [2 to 13.]

Unlike previously described preponderance of small for dates and small head size noted with 10q deletions, our infant was appropriate for gestational age (AGA) in all growth parameters including head circumference (57th%ile). His dysmorphic / clinical features that included sloping frontal bone, hypertelorism, flattened nasal bridge, and right cryptorchidism, were already described in previous reports. He also had the previously unreported findings including atypical Pierre- Robin sequence (bilateral "V" shaped cleft of soft and hard palates (not reverse "U-shaped), micrognathia and Glossoptosis), cleft lip only on the left side, and bilateral dorsal horn ventriculomegaly (unusual finding in a term infant).

Age at diagnosis and gender:

There were only a few reported cases of deletions of 10q that were prenatally diagnosed / suspected (noted between 16 and 29 weeks), and confirmed postnatally [12, 15, 16]. Our infant had antenatal diagnoses of suspected unbalanced translocation of chromosomes 10 and 12, and fetal cleft lip and cleft palate. Postnatally, he was proven to have 10q interstitial deletion. Most of the neonatal cases that were diagnosed with 10q deletions shortly after birth, had dysmorphic features that prompted testing for genetic abnormalities [2, 7, 11, 17]. Majority of the children in the age group of 1 to 5 years that were diagnosed to have 10q deletions, were originally referred to genetics teams, because of undiagnosed dysmorphic features, and severe developmental delays [3, 6, 13, 17, 18]. Unlike adults, there was no strong gender predisposition among pediatric cases [2, 8, 9, 11]. There was a significant representation of teens among those that were diagnosed with 10q deletions [2, 6, 8, 17]. Adults that were assessed because of severe cognitive delay, and noted to have 10q deletions, seemed to have a high female preponderance [6, 13, 19]. Their age at diagnosis among reported cases of adults ranged between 29 and 63 years [6, 19, 20].

Genetic and Clinical implications of 10q deletions:

Chromosome microarray analysis (CMA) along with array comparative genome hybridization, and single nucleotide polymorphisms arrays (SNP) is often used as the first line of testing for children with developmental delay/cognitive delay. Chromosome 10q terminal deletions can encompass deletions noted at variable locations and sizes. To correlate various phenotypes with the critical region (CR) on the chromosome, more sophisticated tests are needed. Most of the

previously reported cases used traditional techniques including G- banded karyotyping, fluorescence in situ hybridization (FISH), and microsatellite marker genotyping [13]. Newer group of studies include CMA based molecular investigations, such as high resolution single-nucleotide polymorphism (SNP) analysis.

In 1989, from their review of 18 cases of terminal 10q syndrome, Wulfsberg et al [5] were first to show the direct correlation between the severity of malformations and size of the deleted segment of the chromosome. In 2009, using a combination of standard chromosome banding, and FISH (using YAC probes), Irving et al [6] analyzed 15 new cases of distal 10q deletions involving regions of 10q25 to 10q27 (Our infant's deletion was at 10q25.1 to 10q26.1). Of those, 8 were familial cases of terminal deletions, 4 were de novo terminal deletions, and 3 were de novo interstitial deletions. They found that the most consistent clinical features in these patients were facial anomalies including facial asymmetry, prominent nose and nasal bridge, prominent ears, thin upper lip, growth restriction, developmental delay, and digital abnormalities. Varying degrees of learning difficulties were also found in 11 cases and behavioral problems were noted in 4 out of 15 cases.

The severity and clinical characteristics of patients with a deletion in this region vary widely, not only due to the length of deletion, but also based on location of the deletion. Faria et al [9], and Yatsenko et al [13], postulated that DOCK1 is the smallest region of overlap (SRO I) that was responsible for clinical signs (phenotype). Faria et al also suggested a second 3.5 Mb region (SRO II) was also important for the presentation of the phenotype. They postulated that cranio-synostosis was not directly related to dysregulated signaling in suture development. Probably it might be secondary to alterations in brain development. Genes at 10q26 were implicated in the molecular crosstalk between brain and cranial vault. Our baby's 10q interstitial deletion was 13.3 Mb (larger), encompassing 71 RefSeq and OMIM genes.

In 2015, Vera- Carbonell et al [18] compared phenotypical features of their 3 patients with other cases, reported to have had isolated deletions. Based on that observation, they postulated that small 10q26.2 terminal deletions might be associated with growth retardation developmental delay / intellectual disability, craniofacial features, and external genital anomalies, and longer terminal deletions affecting 10q26.12 and/or 10q26.13 regions might be responsible for renal/urinary tract anomalies. In 2015, Choucair et al [8] suggested the possibility of two new SROs (smallest region of overlap), one associated with microcephaly, growth and psychomotor disorders and the second one associated with genital anomalies. They suggested that "*FGFR2, NSMCE4A,* and *ATE1* genes were responsible for facial dysmorphism, growth cessation, and heart defects respectively. *WDRII* was linked to idiopathic hypogonadotropic hypogonadism, and Kallman syndrome". They postulated that its haplo-insufficiency could play a role in the genetic anomalies.

Ogata et al [17] in a series of 10 cases of distal 10q monosomy (6 males and 4 females) used FISH and whole chromosome painting for confirmation (cases 1- 8). Microsatellite analysis showed urinary tract anomalies were common, if the hemizygosity was distal to D10S186, and genital anomalies were common if it is distal to 10S1248. It was noted that *PAX2, GFRA1* and *EMX* genes are located on distal 10q, and so they postulated that deletions in that region could explain urogenital problems. They reemphasized that monosomy for the distal 10q was frequently associated with urogenital anomalies such as vesico-ureteral reflux, (VUR), renal hypoplasia, micropenis, hypospadias, cryptorchidism and hypoplastic labia majora. Persistent mullerian duct syndrome (PMD) with anti-mullerian hormone (AMH) deficiency secondary to mutations or deletions of the *AMH* gene was reported by Tosur et al [7], in association with distal monosomy 10q. Usually PMD is associated with mutations or deletions of

AMHR2 and *AMH,* located on chromosome 12q13 and 19P13.3.

Gunnarsson et al [11] noted that "the 12.5 Mb long deletion of 10q chromosome from cytoband10q26.12 represents at least 100 protein coding genes". Of those, *FGFR2* gene seemed to be important, correlating with birth defects. Mutations of this gene was implicated as the "cause for several dominantly inherited congenital skeletal disorders" such as Crouzon syndrome, Pfeiffer syndrome, isolated coronal stenosis, Apert syndrome, Jackson- Weiss syndrome, and Bear-Stevenson cutis gyrate syndrome. They were also linked with malformations of limb, cardiac, CNS and trachea. Among the congenital cardiac defects, PDA, VSD and ASD are most commonly associated with 10q deletions.

Other clinical manifestations linked with 10q deletion syndromes:

In 2000, McCandless et al [20] reported a 48 year old man with interstitial deletion of chromosome 10q25.1q25.3 with clinical findings suggestive of Coffin-Lowry syndrome (severe cognitive delay, short stature, coarse facial features, hypertelorism, and patulous lips). Rasheed et al [21] reported a loss of 10q in 15 human gliomas. Maier et al [22], showed somatic deletion mapping on chromosome 10 and sequence analysis of *PTEN/MMAC1* (tumor suppressor genes) point to the 10q25-26 region as the primary target for both low grade and high grade gliomas. As early as in 1993, Fults et al [23], showed that a loss of one entire copy of chromosome 10 could be a genetic link with glioblastoma multiforme, the most malignant glial brain tumor. Allelic deletions are suggestive of loss of tumor suppressor genes, a common event noted in Endometrial cancer (EC), the most common gynecologic malignancy in western countries. Baldinu [24] reported the presence of a gene *CASC2* in allelic loss, at chromosome 10q26 inhuman endometrial cancer.

A literature search (OMIM) [4] of the missing 71 genes secondary to the interstitial deletions of 10q of our infant revealed that the deleted genes are linked with a predisposition for various neoplasms (some are malignant), apoptosis, cerebral palsy, CNS malformations, pancreatic lipase deficiency, and syndromes with severe cognitive delays (refer to the supplement-appendix).

Limitations:

This report's main limitation was lack of parental consent for further testing. Henceforth, we couldn't conclude about its de novo presentation. One could also argue that the infant's novel features such as atypical Pierre-Robin sequence with cleft lip and bilateral dorsal horn ventriculomegaly (unusual in a term infant) could be coincidental. But, there was a case report (OMIM 604294) [4] of dorsal ventriculomegaly in an Egyptian male infant with bilateral severe microphthalmia and small optic nerves, bilateral cleft lip and palate, and agenesis of the corpus callosum (*MCOPS11*). Such an involvement of central nervous system (CNS) was noted to be associated with deletions of genes such as *EMX2* (OMIM 600035), *ADD3* (OMIM 601568), and *SHOOTN1* (OMIM 611171) noted in our patient's deleted segment (refer to appendix).

CONCLUSION

Here, we reported a very unusual case of a dysmorphic male newborn with an interstitial deletion within the long arm of chromosome 10 between bands 10q25.1 and 10q26.1, along with a few suggested new associations. In addition to presenting a case report, we have presented a comprehensive review of literature on chromosome 10q's both terminal and interstitial deletions. Earlier detection of both common and rare chromosomal- genetic abnormalities may prepare the family and health care team to plan optimal care to the mother, baby and the family. We anticipate cost saving and improving parent-infant bonding measures such as telemedicine [25] playing a major role in such clinical situations.

In our supplement- appendix, we also listed the clinical implications of 71 RefSeq and OMIM genes noted in that ~13.3Mb 10q interstitial

deletion. This extensive literature search revealed the importance of chromosome 10q, which seemed to involve many medical subspecialties, including oncology. Despite their rarity, routine referral to a level IV perinatal center (due to the availability of maternal fetal medicine specialists and geneticists), needs to be considered in a high prevalence geographical region, for even apparently common anatomical abnormalities of the fetuses such as cleft lip, cleft palate, atypical Pierre- Robin sequence, and CNS anomalies. Also, further reports of patients with 10q25 or 10q26 region deletions can help to determine the exact phenotype that corresponds with each specific gene deletion.

Contributions:

Raja Nandyal--1, 2 and 3 (Substantial contributions to conception and design, acquisition of data, main author of manuscript, proof reading and final approval)

Sara Hagan--1, 2 and 3 (acquisition of data, co-author of manuscript, and final approval)

Tavleen Sandhu—1, 2, 3 (acquisition of data, co-author of manuscript, proof reading, final approval)

1) Substantial contributions to conception and design, data analysis design and interpretation of data.

2) Drafting the article or revising it critically for important intellectual content; and

3) Final approval of the version to be published.

Financial Interests and Conflicts:

Raja Nandyal has no financial interests or conflicts to disclose

Sara Hagan has no financial interests or conflicts to disclose

Tavleen Sandhu has no financial interests or conflicts to disclose

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APPENDIX:

The size of the interstitial deletion is ~13.3Mb encompassing 71 RefSeq and OMIM genes.

Deleted genes without OMIM numbers:

SORCS3, SORCS3-AS1, LOC101927549, LOC105378470, SORCS1, LINC01435, XPNPEP1, ADD3-AS1, ADD3, MXI1, SMNDC1, DUSP5, SMC3, RBM20, PDCD4-AS1, PDCD4, MIR4680, BBIP1, SHOC2, RPL13AP6, MIR548E, ADRA2A, GPAM, TECTB, MIR6715B, MIR6715A, GUCY2GP, ACSL5, ZDHHC6, VTI1A, MIR4295, LOC103344931, TCF7L2, SNORA87, HABP2, NRAP, CASP7, PLEKHS1, MIR4483, DCLRE1A, NHLRC2, ADRB1, CCDC186, MIR2110, TDRD1, VWA2, AFAP1L2, ABLIM1, LOC101927692, FAM160B1, TRUB1, LOC102724589, ATRNL1, GFRA1, CCDC172, PNLIPRP3, PNLIP, PNLIPRP1, PNLIPRP2, C10orf82, HSPA12A, ENO4, SHTN1, VAX1, MIR3663HG, MIR3663, KCNK18, SLC18A2, PDZD8, EMX2OS, and EMX2.

Clinical Implications of the deleted genes (linked to **OMIM** data):

Sequentially listed OMIM number, discussed gene and available clinical information.

OMIM 606285- *SORCS3*

OMIM 606283- *SORCS1*

OMIM 602443- *XPNPEP1*

OMIM 601568- *ADD3*- Spastic quadriplegia cerebral palsy

OMIM 600020- *MXI1*- Glioblastomas, astrocytomas, prostate cancer, neurofibromatosis

OMIM 603519- *SMNDC1*

OMIM 603069- *DUSP5*- Endothelial cell apoptosis.

OMIM 606062- *SMC3*- Cornelia de Lange syndrome

OMIM 613171- *RBM20*- Dilated cardiomyopathy

OMIM 608610- *PDCD4*- Apoptosis, Colorectal cancer

OMIM 613605- *BBIP1*- Bardet-Biedl syndrome (severe form of *MKS1* disorder- Meckel-Gruber syndrome frequently has cleft lip and cleft palate)

OMIM 602775- *SHOC2*- Noonan syndrome like disorder with loose anagen hair

OMIM 104210- *ADRA2*- Spontaneous abortions (alpha-2-adrenoceptors-> essential at the placental interface between mother and embryo to establish the circulatory system of the placenta and thus maintain pregnancy)

OMIM 602395- *GPAT*

OMIM 602653- *TECTB*- Cochlear sensitivity

OMIM 605677- *ACLS5*- Primary gliomas of grade IV malignancy

OMIM 614316- *VTI1A*- Colorectal cancer

OMIM 602228- *TCF7L2*- Colorectal cancer, susceptibility to non-insulin dependent diabetes mellitus.

OMIM 603924- *HABP2*- Susceptibility to non-medullary thyroid cancer and venous thromboembolism (Factor VII – activating protease polymorphism)

OMIM 602873- *NRAP*- Nebulin- related anchoring protein within the sarcomeres of skeletal muscle

OMIM 601761- *CASP7*- Apoptosis

OMIM 609682- *DCLRE1A*- Apoptosis

OMIM 109630- *ADRB1* gene- autoantibodies against the beta-1-adrenergic receptor in some patients with idiopathic dilated cardiomyopathy.

OMIM 605796- *TRD1*- Male infertility

OMIM 612420- *AFAP1L2*

OMIM 602330- *ABLIM1*- Retinal rods

OMIM 617312- *FAM160B1PNLIPRP1*-

OMIM 610726- *TRUB1*- Dyskeratosis Congenita 1

OMIM 612869- *ATRNL1*

OMIM 601496- *GFRA1*- Hirschsprung disease

OMIM 246600- *PNLIP*- Pancreatic lipase deficiency

OMIM 604422- *PNLIPRP1*- Pancreatic lipase related protein 1 (a key function in dietary fat absorption)

OMIM 604423- *PNLIPRP2*- Pancreatic lipase related protein 2

OMIM 610701- *HSPA12A*- Atherosclerosis

OMIM 611171- *SHOOTN1* gene- involved in the generation of internal asymmetric signals required for neuronal polarization.

OMIM 604294- *VAX1* gene- a case report of an Egyptian boy with bilateral severe microphthalmia and small optic nerves, bilateral cleft lip and palate, and agenesis of the corpus callosum (MCOPS11)

OMIM 613655- *KCNK18* gene- autosomal dominant transmission of migraine with aura, and K leak

OMIM 193001- *SLC18A2*- Infantile Parkinsonism- Dystonia 2

OMIM 614235- *PDZD8* gene suppresses HSV-1 infection, but promotes HIV-1 infection

OMIM 607637- *EMX2OS*- A putative endometrial tumor suppressor gene (*EMX2OS*- Noonan et al)

OMIM 600035- *EMX2*- Schizencephaly, endometrioid adenocarcinomas and a mullerian mesodermal tumor