Neuronal migration genes and a familial translocation t(3;17): which genes are implicated in the phenotype?

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Abstract
Background: While Miller-Dieker syndrome critical region deletions are well known delineated anomalies, submicroscopic duplications in this region have recently emerged as a new distinctive syndrome. So far, only few cases have been described overlapping 17p13.3 duplications. Methods: In this study, we report on clinical and cytogenetic characterization of two new cases involving 17p13.3 and 3p26 chromosomal regions in two sisters with familial history of lissencephaly. Fluorescent In Situ Hybridization and array Comparative Genomic Hybridization were performed. Results: A deletion including the critical region of the Miller-Dieker syndrome of at least 2.9 Mb and a duplication of at least 3.6 Mb on the short arm of chromosome 3 were highlighted in one case. The opposite rearrangements, duplication 17p13.3 and deletion 3p were seen in the second case. This double chromosome aberration is the result of an adjacent 1:1 meiotic segregation of a maternal reciprocal translocation t(3;17)(p26.2;p13.3). Conclusions: 17p13.3 and 3p26 deletions have a clear range of phenotypic features while duplications still have uncertain clinical significance. However, we could suggest that regardless of the type of the rearrangement, the gene dosage and interactions of CNTN4, CNTN6 and CHL1 in the 3p26 and PAFAH1B1, YWHAE in 17p13.3 could result in different clinical spectrums.

Background
The presence of clinical practice in the diagnosis of human chromosome abnormalities including gain or loss of genomic copy numbers has extremely benefited from the development of advanced molecular cytogenetic methods such as array-CGH. This allows high-resolution pangenomic analysis, in particular in detecting genetic imbalances, defining their size, delimiting translocation breakpoints and analyzing the involved segments [1]. Array-CGH has identified novel co-locating micro-deletions and micro-duplication in the same locus. This allowed describing new genomic disorders leading to distinct different clinical phenotypes. Recently, the duplication of the entire Miller-Dieker syndrome critical region (MDS) involving PAFAH1B1 and YWHAE genes, and new co-locating micro-duplications in chromosome 17p13.3 have been defined within, duplication syndromes in the MDS locus [2–3]. Likewise, deletions and duplications of 3p26 region were described as new emerging syndromes [4–5–
In this study, we report a familial translocation (3;17) leading to two different cytogenetic rearrangement resulting in a duplication/deletion of the 17p13.3 critical region for MDS including *PAFAH1B1* and *YWHAE* genes and 3p26 region including *CNTN4, CNTN6, CRBN* and a part of *CHL1*. Duplication and deletion of the same chromosomal region resulted in a distinct phenotypic feature in the offspring.

**Methods**

**CLINICAL REPORT**

**Patient 1 (the proband)**

A 2-year-old girl referred for the cytogenetic exploration of a family history of lissencephaly (FIG. 1), is the second child of a healthy consanguineous Tunisian couple. The patient’s weight at birth was 3,500 g (+0.6SD). She measured 52 cm (+1.05DS) and had a head circumference of 35 cm (+0.4SD). At 2 years of age, her height and head circumference were 88 cm (+0.9SD) and 45 cm (-2.5SD), respectively. At physical examination, she had psychomotor development delay and abnormal behavior including aggressiveness, anger and agitation. Furthermore, she had craniofacial dysmorphic features (FIG. 2) including a long face, high forehead, down-slanting palpebral fissures, epicanthus, wide nose, long philtrum, thin upper lip, large and high implanted ears and pointed chin with micrognathia. In addition, she showed arachnodactyly. Her cerebral magnetic resonance imaging (MRI) was performed at two years and five months of age, and corpus callosum hypoplasia was detected.

**Patient 2**

The patient presented at 4 months for exploration of growth retardation, axial hypotonia, seizure and dysmorphic features (FIG. 2) including high forehead, wide nose, low implanted ears and lissencephaly at MRI. She died 10 months later. Her brother (II1) (FIG. 1) suffering from type 1 lissencephaly, died also at an early age of life.

**Karyotype**

Metaphase chromosome preparations were obtained by phytohemagglutinin (PHA) stimulated
lymphocyte culture according to standard procedures. Chromosome analysis was carried out applying R-bandig at a 500-band level according to ISCN 2016 [7] in the patient, parents and sister.

*Fluorescent in situ Hybridization (FISH)*

FISH was performed on blood lymphocytes blocked on metaphases of the patient, those of her sister and those of her mother, according to the standard protocol. Two probes screening the chromosome 17 short arm and the chromosome 3 short arm were used: commercial probes; Miller-Dieker/Lissencephaly region probe set: LSI (Red) and RARA (Green) (Vysis) (Abbott Laboratories, IL, USA) and Totel Vysion Multicolor DNA Probe Mixture 3 (Vysis®, Downers Grove, Illinois, USA) containing 3ptel (Green), 3qtel (Red), 22q (Orange and Green) and LSI BCR (22q11) (Aqua).

The hybridized chromosomal spreads were analyzed using a fluorescent microscope equipped with appropriate filters and Cytovision FISH system image capture software (Zeiss Axioskop 2 plus). Slides were scored on the basis of the number of probe signals for each metaphase. For each target area ten hybridized metaphases were analyzed.

*Array CGH*

Oligonucleotide array CGH was performed using the Agilent Human Genome CGH Microarray Kit 44K®. This microarray consisted of more than 44,000 oligonucleotide probes that spanned both coding and non-coding regions. The coverage of the human genome was made with an average spatial resolution of 75,000 pair bases.

The patient’s DNA as well as a reference DNA was fragmented by heat at 95°C for 20 minutes. Each fragmented DNA product was labeled by random priming using either ULS5 or ULS3. After column-purification, probes were denaturized and pre-annealed with 5 μg of human Cot-1 DNA, 10 μl of CGH Blocking agent and 55 μl of hybridization buffer. Hybridization was performed at 65°C during 24 h. The microarray was washed, scanned and analyzed with Agilent Feature Extraction® 9.1 software. Results were interpreted with DNA analytics® 4.5 software. Only imbalances involving three or more adjacent probes were held. The identification of probes with a significant gain or loss was based on the log² ratio plot deviation from 0 with cutoff values of 0.5 to 1, and −0.5 to −1, respectively.

*Results*
The conventional cytogenetic analysis did not reveal any chromosomal anomalies in the two sisters and parents’ karyotypes.

FISH was first performed on the sister (FIG. 1.117) using subtelomeric probes (Vysis) of chromosome 17p showed the absence of a subtelomeric signal on one of the chromosomes 17p (FIG. 3.A). This was suggestive of a family subtelomeric translocation (FIG. 4).

Consequently, using the same probe of chromosome 17p, FISH analysis showed hybridization on the derivative chromosome 3 and on normal chromosome 17 (FIG. 3.B/C), 46,XX.ish t(3;17)(p26.2;p13.3) (LIS1+,subtel3ptel+,subtel3qter+) in the mother.

FISH was then performed in the proband using 17p probe and showed three signals on the two normal chromosomes 17 and the derivative chromosome 3. This confirmed the duplication of the terminal region of chromosome 17. Mixture 3 (Totel Vysion) was used to characterize this rearrangement. In fact, FISH performed on the metaphasic lymphocytes of patient’s and mother’s blood demonstrated the translocation between 17pter and 3pter (FIG. 3.C/E).

Ideograms of maternal chromosomes 17 and 3 illustrate the exchange of chromosome material of 17ptel and 3ptel regions due to the reciprocal translocation t(3;17). The patient 1 inherited the der(3) mat and the normal paternal chromosomes 17 and 3. The patient 2 inherited the der(17) mat and the normal paternal chromosomes 17 and 3.

Aiming to delimit the involved segments, array-CGH analysis was performed on the proband and showed a large deletion of 3,6 Mb on the short arm of chromosome 3, involving 12 OMIM genes and a large duplication of 2,9 Mb on the short arm of chromosome 17, encompassing 61 OMIM genes: 46,XX.arr[GRCh18]3p26.2(224727_3864822)X1,17p13.3(48539_2976723)X3 mat (FIG. 5).

Discussion
Adjacent 1 segregation of the translocation t(3;17) in the mother led to two different chromosome imbalances in the children. The first type adjacent 1 gave rise to a derivative 3 chromosome (der3) in patient 1 that resulted in partial monosomy 3p and a partial trisomy 17p. While the second adjacent 1 type led to a derivative 17 (der17) in patient 2 that resulted in partial monosomy 17p and a partial trisomy 3p. 17p13.3 deletion encompassed PAFAH1B and YWHAE genes.
While deletions of 17p13.3 are associated with well-known phenotype ranging from Miller Dieker syndrome [8] to partial callosal and milder phenotype [9], duplications of the same chromosomal region still need further clinical and molecular characterization.

So far, to the best of our knowledge, only 13 patients having large 17p13.3 duplications, including the entire MDS comprising both PAFAH1B1 and YWHAE genes have been reported [10–11–2–12–13–14–15–16] (FIG. 6). Interestingly, all submicroscopic 17p13.3 duplications reported to date, including the present case did not share any recurrent breakpoints and have varying sizes. It has also been reported that these duplications might be the result of parental translocations involving chromosome 19 [13], chromosome 10 [14] and chromosome 5 [17] but it has never involved the 3p26 region. The proximal short arm of chromosome 17 is distinctly prone to cryptic rearrangements due to the presence of extensive repetitive sequences [2]. Furthermore, this MDS telomeric critical region is estimated to at least 400kb including eight genes in addition to PAFAH1B1gene [18].

**FIG. 6** Schematic illustration of the molecular findings in individuals reported with duplication in the Miller Dieker Syndrome (MDS) Critical Region encompassing both YWHAE and PAFAH1B1 genes. The genomic distances (in base pairs from the 17p telomere) shown at the top of the figure were according to ensemble genome browser 59 (hg18). For each patient, a normal copy number is illustrated as a blue line and the duplicated segment as a pink line.

Due to the variability of the involved genes, 17p13.3 duplications have been divided into two classes with distinct phenotypic features [2]. While, Class I duplications involve only YWHAE gene including autistic manifestations, speech, motor delay and dysmorphic facial features, Class II duplications include necessary PAFAH1B1gene and may contain also YWHAE and CRK genes [2]. The phenotypic features in these cases show moderate to mild developmental and psychomotor delay [2]. Nevertheless, when all the three genes, YWHAE, CRK and PAFAH1B1 are duplicated, the phenotype seems to be more severe [10].

Here, our proband shared clinical and dysmorphic features described in patients with duplication of the complete MDS region such as abnormal behavior (Table 1).

We reviewed an exhaustive list for the selection of thirteen cases of 17p13.3 trisomic (Table 1) who
showed common dysmorphic features including a high forehead, a small mouth, and a triangular chin. Some of these features were absent in our patient. In addition, our patient presented arachnodactyly, which is rarely described in patients with partial trisomy of 17p13.3 [10-2-12-17]. By means of complementary cytogenetic techniques, the chromosomal rearrangements were estimated to at least 3.6 Kb on chromosome 3p26.2 and 2.9 Mb on chromosome 17p13.3. The most frequent phenotypic features associated with partial trisomy 17p13.3 were correlated with duplication of the PAFAH1B1 and YWAHE genes that were located in the MDS region. It was hypothesized that the duplication of YWAHE might have an effect on neuronal network development and maturation, and was related to mild development delay and facial dysmorphisms while the duplication of PAFAH1B1 that lead to its overexpression, was associated with moderate to severe development delay and structural brain abnormalities [10-2]. Brain-imaging analysis was performed in seven of the eleven reported patients and only four showed structural brain abnormalities (Table 1). Corpus Callosum hypoplasia or agenesis represented the main brain abnormality being frequently described [10-14-11-15].

Likewise, our patient presented corpus callosum hypoplasia. Curiously, patients having the smallest and the largest duplications of the entire MDS region reported so far have presented normal Magnetic Resonance Imaging (MRI) (P1/[11]; P1/[16]). This suggests that this heterogeneity depends on the size of the duplication and the involved genes as well as on the involvement of other gene interactions and modifier genes. Indeed, it has been proven that transgenic mice with increased lis1 expression in the developing brain revealed abnormalities in the neuroepithelium such as the thinning of the ventricular zone, and the ectopic positioning of mitotic cells [10]. Furthermore, lis1 overexpression affected both radial and tangential migration. In fact, in this condition, migration delay in both trajectories was observed: radial migration at E13.5 and tangential migration at E12.5 rather than E14.5 [10]. However, subtelomeric neuronal migration defects are not expected to be detected by MRI scans [10]. Consequently, we can postulate that the overexpression of LIS1 gene could explain the phenotype of our patient particularly corpus callosum hypoplasia.

The clinical findings in this case are certainly due to the cumulative effect of two imbalances as the result of adjacent-1 malsegregation in the maternal balanced translocation. Numerous features might
be attributed to genes that are lost in chromosome 3p in addition to 17p13.3 duplication. In fact, it has been shown that terminal 3p deletions cause a wide range of phenotypes and are responsible for a rare contiguous gene disorder (OMIM# 613792). This syndrome is characterized by a recognizable phenotype including postaxial polydactyly, renal abnormalities, moderate bilateral sensorineural hearing loss, bilateral macular hypoplasia, respiratory difficulties, hypoplastic corpus callosum, congenital heart defect and gastrointestinal abnormalities [19–20]. The severity of the phenotype depends on the size of the deletion as well as on the gene content and disrupted genes involved in the breakpoints [19].

The proposed pathogenic mechanism for this syndrome is the haploinsufficiency of three important genes (CNTN4, CNTN6 and CRBN) (FIG. 7) leading to developmental delay or mental retardation [21–22–23]. It has been demonstrated that both CNTN4 and CNTN6 genes encode a neural adhesion molecule that is part of the immunoglobulin superfamily [24–25]. In fact, the CNTN6 gene plays a crucial role in the development, maintenance, and plasticity of functional neuronal networks in the central nervous system. It has been shown that Cntn6 deficiency in mice causes profound motor coordination abnormalities and learning difficulties [26]. Owing to its function, we suggest that CNTN6 gene could be responsible for the observed psychomotor development retardation in the current case. On the other hand, CNTN4, an important gene for brain development, is known to be involved in axon growth, guidance, and fasciculation [27–28–29–30]. In addition, it probably contributes to the behavioral abnormalities in our patient showing aggressiveness, anger and agitation. In fact, knockout mice of homologous neuronal adhesion molecules showed morphological, neurological and behavioral abnormalities [31].

The deletion included also CRBN gene encoding a protein of the ubiquitin proteasome pathway, which seemed to play a crucial role in brain development [32] (FIG. 7). In fact, CRBN protein is part of DCX protein ligase complex involved in the regulation of the surface expression of certain types of ion channels in neuronal memory synapses. Furthermore, the 3p26 deletion disrupted a more distal gene: CHL1 (FIG. 7). The latter encodes a protein member of the L1 family of neural cell adhesion molecules [33] and plays a crucial role in development of cortex by regulation of neuronal differentiation and
axon guidance [34–35] and is involved in the maturation of nervous system by regulation of synaptic activity and plasticity [36–37]. Previous studies suggested CHL1 as a dosage-sensitive gene with a main role in intellectual disabilities [21–38–39–40]. Interestingly, Frints hypothesized that reduction equal to 50% of chl1 in the developing brain marks cognitive deficit [21].

FIG. 7 Schematic representation of the 3p26.3->pter chromosomal subtelomeric region, with the locations of genes

Haploinsufficiency of CNTN4, CNTN6 and CRBN and disruption of CHL1 within the breakpoints could then be responsible for the observed neurodevelopmental phenotype in the proband.

We reviewed six previously reported cases having 3p deletion, compared them to the present case report, and noted that the most frequent features are microcephaly, corpus callosum hypoplasia and facial dysmorphia (Table 2). Conversely, some studies reported cases with 3p deletion and normal phenotypes [45–46–20]. In other studies, the authors have even hypothesized that the distal 3p deletion is probably associated with normal intelligence and normal physical features [47-41]. Interestingly, both 3p deletion and 17p duplication could share the same network in neuronal migration since both anomalies lead to corpus callosum hypoplasia and pachygyria. So far, both genes duplicated in 17p especially PAFAH1B1 and genes deleted in 3p especially CNTN6 and CRBN affected the process of cortical development by alteration of the stabilization of microtubules, the axon growth and the axon guidance [48–26–49].

Neuronal migration is a complex process that involves several actors and factors [50–51]. The most critical step responsible for a normal brain development is the cell migration from the ventricular zone into the cortical plate [52].

Mutations and chromosomal aberrations can alter the chromosome 3D organization. This alteration could play a more important role than we believe it does in chromosomal interactions and transcriptional regulation of genes. In fact, it has been shown that the chromatin 3D modification could disturb the topologically associating domains (TADs) and consequently the regulation of gene expression [53–54–55]. Such alteration could explain the phenotypic variability in human disease ranging from milder phenotype to microdeletion/microduplication syndrome.
Conclusions
The variability of genes, which are mapped in the involved regions (3p and 17p), and the description of the clinical characteristics of our patient contribute to the confirmation and further delineation of the associated characteristics to the partial trisomy of 17p13.3 encompassing the entire MDS critical region as well as the partial monosomy of chromosome 3p26.2. Various genes and structural chromosomal anomalies have been discovered involved in this process. However, the exact molecular basis of brain malformations still needs further studies.

Abbreviations

CNTN4: contactin 4; CNTN6: contactin 6; CHL1: close homolog of L1; PAFAH1B1: platelet activating factor acetylhydrolase 1b regulatory subunit 1; YWHAE: tyrosine 3-monoxygenase/tryptophan 5-monoxygenase activation protein epsilon; Array CGH: Array comparative genomic hybridization; SD: standard deviation; ISCN: International System for Human Cytogenetic Nomenclature; OMIM: Online Mendelian Inheritance in Man; CRK: v-crk avian sarcoma virus CT10 oncogene homolog; CRBN: cereblon;

Declarations

Ethics approval and consent to participate
This study was approved by the local Ethics Board of the University Teaching Hospital Farhat Hached.

Written informed consent to participate in this study was obtained from the parents.

Consent to publish
Written informed consent was obtained from the parents for photo and clinical data publication.

Availability of data and materials
All data generated or studied during this study are included in the published article which is available upon request from the corresponding author.

Competing interests
All the authors have no competing interests.

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Authors’ contributions
SMZ contributed to conception and design. MHA, SD and HH contributed to all experimental work,
analysis and interpretation of data. KBH and AM referred patients to our department. SMZ and SD were responsible for the consultation. SMZ and AS were responsible for overall supervision. MHA drafted the manuscript, which was revised by SMZ. All authors read and approved the final manuscript.

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Tables

Table 1 Comparison of the phenotypic features with duplication of Miller-Dieker completed region

| Patient reference | Paper | [13] | [16] | [12] | [11] | [10] | [15] | [Pat] |
|-------------------|-------|------|------|------|------|------|------|------|
| Size of duplication, Mb | Patient 1 | 10.7 | 5.77 | 4.2 | 4 | 3.6 | 3.4 | 3 |
| Inheritance | maternal | De novo | ? | De novo | De novo | De novo | De novo | pat |
| Age at diagnosis, years | prenatal | 4 | 13 | 1 | 10 | 28 | 0 |
| Gender | F | F | F | M | F | F |
| Birth height, cm | NA | 55 | Normal | 50 | 53 | NA |
|-----------------|----|----|--------|----|----|----|
| Birth weight, g  | NA | 2680 | Normal | 3380 | 3060 | NA | 3 |
| Current height   | NA | +1SD | +1SD | +1SD | +1SD | NA | 50-perc |
| Current weight   | NA | +1SD | +1SD | +1SD | +2SD | NA | 2 perc |
| Cranio-facial dismorphism Hypotonic face | NA | + | + | + | - | + |
| Broad midface    | NA | NA | + | + | - | - |
| High forehead    | + | + | - | + | - | NA |
| Upward palpebral fissures | NA | + | - | - | + | NA |
| Hypertelorism m  | NA | + | + | + | - | - |
| Epicanthus       | NA | NA | NA | + | NA | NA |
| Strabismus       | NA | NA | - | - | + | NA |
| Broad nasal bridge | NA | + | + | + | - | NA |
| Small mouth      | NA | + | + | + | Normal | + |
| Low-set-ears     | + | NA | - | - | - | NA |
| Triangular chin  | NA | NA | + | + | NA | + |
| Neck appearance  | NA | NA | Normal | Short | Normal | NA | Short |
| Limb abnormalities | NA | NA | + | - | - | - | Long |
| Hip luxation     | NA | NA | - | + | - | NA |
| Equinovalgus     | NA | NA | - | Right | - | NA |
| Neurological features Hypotonia | NA | + | + | + | - | NA |
| Delayed mental development | NA | + | + | + | + | LD |
| Delayed motor development | NA | + | + | + | + | + |
| Abnormal behavior | NA | NA | + | + | + | NA |
| Brain imaging results | NA | Normal | Normal | Dilated lateral ventricles/ Corpus Callosum Agenesis | Reduced brain size, Corpus Callosum Hypoplasia, | NA | Cc Atrio Hypo Cc Cal |
| Paper | [ 4 ] | [ 41 ] | [ 42 ] |
|-------|-------|-------|-------|
| Patient reference | Patient 1 | Patient 1 | Patient 2 |
| Size of deletion, Mb | 4.5 | 1.5 | 1.05 |
| Inheritance | De novo | paternal | maternal |
| Age at diagnosis, years | 16 | 9 | 24 |
| Gender | M | M | M |
| Birth height, cm | 71 | 123 | 58 |
| Birth weight, g | 2695 | 2600 | 5350 |
| Current height | NA | NA | -2SD |
| Current weight | NA | NA | -2SD |
| Cranio-facial dismorphism | + | NA | + |
| Upward palpebral fissures | NA | NA | NA |
| Hypertelorism | + | NA | NA |
| Blepharophimosis | + | NA | NA |
| Eyelid | + | + | NA |
| Broad nasal bridge | + | NA | + |
| Micrognathia | + | NA | NA |
| Low-set-ears | + | NA | + |
| Short philtrum | - | NA | + |
| Limb abnormalities | - | - | - |
| Ptosis | + | + | NA |
| Microcephaly | + | + | + |
| Neurological features | + | + | + |
| Hypotonia | | | |
| Delayed mental development | + | + | + |
| Delayed motor development | NA | NA | + |
| Abnormal behavior | NA | NA | NA |
| Brain imaging results | NA | Centrotemporal spikes in the left hemisphere | Corpus callosum |

Table 2 Comparison of the phenotypic features with deletion 3p26

Figures
Figure 1
Pedigree of the family

Figure 2
Photographs of the patients
FISH analyses A. FISH on sister’s lymphocytes shows no hybridization to chromosome 17 using commercial Miller Dieker/Lissencephaly region probe set: (Lsi LIS1: Red and Lsi RARA: Green) demonstrating the retention of LIS1 gene (green arrow). B. FISH on mother’s lymphocytes using the same commercial probe: (Lsi LIS1: Red and Lsi RARA: Green), shows 2 red spots corresponding to LIS1 gene on one short arms of chromosome 17 and one on chromosome 3 showing the translocation between the short arm of chromosome 17 and the short arm of chromosome 3 (green arrow). C. FISH on mother’s lymphocytes using the commercial probe Totel Vysion (mix 3): (3ptel: Green, 3qtel: Red, 22q Orange and Green, LSI BCR (22q11): Aqua) shows the translocation between the short arm of chromosome 3 (orange arrow) and the short arm of chromosome 17 (green arrow). The 3p probe signal was observed on the short arm of one chromosome 3 (red arrow) and on the short arm of one chromosome 17 (green arrow). D. FISH on proband’s lymphocytes using the commercial Miller Dieker/Lissencephaly region probe set: (Lsi LIS1: Red and Lsi RARA: Green), shows the presence of three red spots confirming the duplication of LIS1 gene (orange arrow). E. FISH on proband’s lymphocytes using the commercial probe Totel Vysion (mix 3): (3ptel: Green, 3qtel: Red, 22q Orange and Green, LSI BCR (22q11): Aqua), demonstrates the deletion of
terminal material from the short arm of chromosome 3 (one green spot).

Figure 4

Ideograms of maternal chromosomes 17 and 3 and their derivatives der(17) and der(3)
Results of 44 K Agilent oligo array-CGH analysis in patient 1. A. chromosome 17, showing 17p13.3 duplication of at least 2.9 Mb in size. B. chromosome 3, showing 3p26.2 deletion of at least 3.6 Mb in size.
Figure 6
Schematic illustration of the molecular findings in individuals reported with duplication in the Miller Dieker Syndrome (MDS) Critical Region encompassing both YWHAE and PAFAH1B1 genes.

Figure 7
Schematic representation of the 3p26.3->pter chromosomal subtelomeric region, with the locations of genes