Neuropsychiatric disorder and gender

Males versus females clinical manifestations with a proximal 16p11.2 copy number variant surrounding gene SH2B1

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Introduction

1. Gender bias in neuropsychiatric disorder:

Gender bias has been repeatedly observed in neurodevelopmental disorders (NDs). Epidemiologic studies in schools and institutions caring for individuals with intellectual disability (ID) have shown a 30%–50% excess of males over females. (1) In autism spectrum disorder (ASD), the male-to-female ratio is 4:1. It increases to 7:1 for high-functioning autism and drops to 2:1 for individuals with moderate to severe ID. (2) X-linked genetic variants have been explored as obvious candidates; however, the frequency of monogenic X-linked disorders in patients who present with NDs is too low to account for the imbalance in the sex ratio. (1, 3) A study of dizygotic twins from population-based cohorts showed that siblings of autistic females exhibit significantly more autistic traits than siblings of autistic males, suggesting that female patients carry a higher genetic burden than male patients. (4) In a large CNV analysis of autistic individuals and their families, Pinto *and al*. found that autistic females were more likely to have highly penetrant CNV and were twice as likely to have exonic deletions involving FMRP (Fragile-X Mental Retardation Protein) targets than autistic males. (5) In cohorts of probands with neurodevelopmental disorders including ASD, we also demonstrate that deleterious autosomal CNV and SNVs were more common in females than in males. (6) Two recent whole exome sequencing (WES) analyses of autism spectrum (AS) confirm this observation. These studies show that both autistic females and males with a low IQ have a high incidence of *de novo* (DN) likely gene disruptive (LGD) mutations. (6) However, there were few DN LGD mutations in high-functioning males with AS. Mutations present in AS males with a low IQ overlap with those found in females but not with those found in AS individuals with a high IQ, demonstrating that sex ratio bias in AS mostly involves high-functioning individuals. These observations suggest that gene disruptive variants, which have been the focus of recent exome studies, are strongly associated with IQ and contribute less to ASD without ID. Studies of specific genomic disorders have also reported gender bias, such as the 2-fold increase in the frequency of males carrying a 16p11.2 deletion or duplication among individuals referred for NDs. (7, 8)

In transmitting parents, we have also showed a significant excess of maternally transmitted deleterious mutations. (6) This is consistent with the sex bias in fecundity

observed in carriers of CNVs in the general population as well as in individuals with schizophrenia. In both groups, the decrease in fecundity is 2 to 3 time more pronounced in males. (9) The cognitive or behavioral traits and mechanisms underlying all of the aforementioned observation remain, however, unknown and will be the focus of our study.

2. Neuropsychiatric disorders and obesity are frequent comorbidities.

Obesity is a frequent comorbidity in individuals with neurodevelopmental disorders (ND), including developmental delay (DD), intellectual disability (ID), and neuropsychiatric diseases like autism, epilepsy, bipolar disease or schizophrenia. (7, 8, 10, 11, 12, 13, 14) Among the many factors underlying the variance of adiposity in our culture, genetics play a key role. (14, 15) Copy number variants (CNVs) at the 16p11.2 locus recapitulate this comorbid presentation with a strong predisposition for obesity as well as cognitive deficits and neuropsychiatric disorders. Different regions (BP1-BP3, BP2-BP3 and BP4-BP5) at the 16p11.2 locus (Figure 1) are susceptible to loss (deletion) or gain (duplication) of genomic copies.

3. Gene-dosage effects in Copy number variants.

We define "gene dosage" effects as the correlation between a trait and the number of genomic copies (deletion=1, controls=2, duplication=3) at a given locus. Beyond the classic case-control design, correlating a phenotype to gene dosage gives additional insight on how a trait is modulated by a gene or a genomic locus. Recurrent CNVs represent a unique paradigm to study the effect of gene dosage, by including in the same analysis deletion and reciprocal duplication carriers as well as intra-familial controls. We used this strategy to demonstrate that dosage effects of the 16p11.2 region (Figure 1) negatively correlates with BMI as well neuroanatomical structures. (7) The BP4-BP5 deletion and duplication each have a general population prevalence of 1/2,000 . CNVs at the BP1-BP3 and BP2-BP3 locus are approximately three times less frequent.

4. Aims:

This study will focus on additional clinical symptoms in a small selected cohort of CNVs. The chromosomal region chosen, more distal of the 16p11.2 locus, is between BP2 and BP3, a second less frequent non-overlapping recurrent CNV encompassing nine genes including SH2B1 (28.73-28.9 Mb). (16) Bokuchova et al have reported an association between deletions encompassing this gene and severe early onset obesity, as well as insulin resistance. SH2B1 is known to modulate the signaling of ligands to JAK-associates cytokine receptors including insulin and leptin but also growth hormone (GH), and nerve growth factors (NGF). (17, 18)

In this research we will concentrate on the CNVs encompassing SH2B1 and build a clinical score, including: malformations, psychiatric diseases, anthropometric features, epileptic seizures, developmental delay and more, in order to analyze the clinical manifestations of a deletion or a duplication of this region and try to find gender differences in clinical phenotypes explaining a « female protective model ». (6)

Methods

Patients

This study was reviewed and approved by the institutional review board of each site conducting the study.

Enrolment of patients was carried out as previously described in Zufferey and al (7). Signed consents were obtained from participants who underwent full assessments. For the data collected through questionnaires, information was gathered retrospectively and anonymously by physicians who had ordered comparative genomic hybridization (CGH) analyses performed for patient care purposes only.

Phenotype data was also collected by contacting clinicians trough the DECIPHER database (19, 20), from the literature (11, 21, 22, 23, 24, 25, 26) and from four different general population cohorts: DECODE (27) EGCUT (28), NFBC66 (29) and SHIP (30).

Data

As previously rationalized, (7) patients with other known genetic diseases or additional CNV were not excluded as it is likely that other additional mutational events that cannot be detected by CGH array or we are unaware of are present in the rest of the dataset. This decision was reinforced by the fact that the exclusion or inclusion of these patients did not change the results significantly.

238 carriers, 108 females and 130 males, of a rearrangement overlapping the SH2B1 gene were included in this study. This includes probands on 16p11.2 BP2-BP3 (n = 140) and BP1-BP3 (n = 23). The 15 BP1-BP5 carriers weren't included in this study since this area also includes the classical 16p11.2 region between BP4 and BP5. To prevent any bias, we separated the relatives from the probands to avoid having more than one member of the same family in a single analysis.

Clinical score

A clinical score (total of 28 points) was calculated for each carrier, based criteria described below.

Malformations score (maximum 9pts)

The clinical score was inspired by De Vries scoring system (36). In our score we decided to include only major malformations. To determine if a malformation described by the physician was major or minor, we used the classification in Uptodate (32). A major malformation has a medical and/or social implication and often needs a surgical repair: microphtalmia, iris or chorioretinal colobomas, cleft palate or lip, cochlear deafness, cardiac ventral or atrial septal defect, congenital heart defect, congenital myocardial hypertrophy, left ventricular dilatation or hypoplasia, cardiac valve insufficiency, Tetralogy of Fallot congenital heart defect, pulmonary stenosis, severe pectus excavatum, hypoplastic extremities, hemivertebra or vertebral hypoplasia, polydactyly, brachymelia, hypospadias and renal agenesis.

To simplify their lecture we categorized them in different systems: **dermatologic**, **ophthalmologic**, **ENT (ears, nose and throat)**, **cardiologic**, **pneumological**, **gastro enterological**, **skeletal**, **neurologic** and **uro-genital**.

Moreover these points included in the score, we analyzed different specific malformations (major or minor) or pathologies that seemed being repeated in our data to analyze if there was as significant impact between males and females.

Points are added if anomalies are present in different categories.

Neuroanatomical score, MRI (maximum 6pts)

MRI data was available for 42 out of 163 probands. CT scan data was available for 1 proband. Neuroanatomical anomalies were classified in the following categories:

- **White matter** anomaly, described as: unmyelinated white matter, cerebral atrophy, hyperintense periventricular white matter, porencephalic cavity at temporo-occipital junction, delayed myelination, cortical atrophy, hyperintense lesions, white matter lesions and hypersignals.
- **Posterior fossa** anomaly, described as: vermis/cerebellar atrophy, Molar tooth sign, minor Arnold Chiari malformation, Dandy Walker malformation and cerebellar arachnoïd cyst
- **Ventricles** anomaly, described as: abnormal broad ventricles, dilated ventricles, and predominance of ventricles and dilatations of the occipital horns.
- **Basal ganglia** anomaly, described as: volume diminution of caudal ganglia and lesion on the right basal ganglia.

- **Corpus callosum** anomaly
- **Other** anomalies that couldn't be classified in one of the classes described above, such as: abnormal hippocampi, lobar holoprosencephaly, left hemisphere malformation and small occipital meningocele.

Points are added if anomalies are present in different categories.

Epilepsy (maximum 1pt)

For all seizures (other than febrile seizure) we attributed one point to the proband.

Psychiatry (maximum 7pts)

Each of the following diagnostic categories were scored as 1 point:
- **Autism spectrum disorder (ASD)**, described as: ASD, Asperger, autistic features/traits and PDD-NOS suspected.
- **Attention deficit hyperactive disorders (ADHD)**, described as: ADHD, hyperactivity and attention deficit (ADD).
- **Anxiety disorders**, described as: anxiety/panic disorders and phobia.
- **Behavior disorders**, described as: behavioral disorder, behavioral regulation problem, tantrum, aggressiveness and obsessive compulsive disorder (OCD).
- **Mood disorders**, described as: depression and bipolar disorder.
- **Psychotic spectrum**, described as: schizophrenia and psychotic.
- **Other**, described as: stereotypic movements, borderline, pica, somatization disorder and self-mutilations.

If a patient had a diagnosed or suspected diagnosis covering one of those groups, it gives him one point for the score. The same patient could have several points in the psychiatric score.

Developmental delay (maximum 2pts)

Motor delay 1 point: It could be specified as **gross** or **fine**. If the patient was not walking at month ≥18 it was considered as a gross motor delay. Language delay, 1 point: When the proband had not said his first word at ≥24 months or fist sentence at ≥32 months. For language delay, further details were often given, so we decided to classify them based on DSM-V neurodevelopmental disorders diagnosis (33). Here are our classification for languages developmental delay :
- **Speech sound disorders** (315.39 DSM-V), described as: not verbal, articulation difficulties/problem, word retrieval problems, dyslalia, dysphasia, expression

difficulties, hard to understand, indistinct speech, phonologic and morpho-synthaxic production difficulties, difficult to understand, fewer words regarding too it's expected age level, executive function difficulties, oromotor dyspraxia, speech sensory processing difficulties, buccolinguofacial dyspraxia, pronunciation difficulties, incomprehensible language, indistinct speech, aphasia, oromotor alteration, hardly any active speech, auditory processing problems, speech sensory processing difficulties, receptive speech difficulties, comprehension difficulties and probably receptive language disorder.

Since the physician's description often couldn't specify if the deficit was receptive or productive, we decided to include both even though the strict diagnosis of Speech Sound Disorder only includes productive disorders.

- **Child-Onset Fluency Disorder** (Stuttering) (315.35 DSM-V), described as: stuttering.

- **Unspecified Communication Disorder** (307.9 DSM-V), described as: mutism.

- **Learning Disorder in Reading** (315.00 DSM-V), described as: dyslexia, difficulty learning to read and cannot read.

- **Learning Disorder in Writing** (315.2 DSM-V), described as: dysgraphia, cannot read and dysorthographia

- **Learning Disorder with mathematic impairment** (315.1 DSM-V), described as: logico-mathematic impairment.

Endocrinology (maximum 1pt)

In 12 probands an endocrinal disorder was described. One point was counted for any diagnosis. Here are the endocrinal pathologies that give a point to the proband: diabetes, growth hormone deficiency, hypothyroid, hyperinsulinemia, hypercalcemia, hypercholesterolemia, hypoglycemia, low testosterone and polycystic ovary syndrome.

Abnormal food behavior (maximum 1pt)

Any food abnormal behavior noticed counted as a point.

Neonatal complications (maximum 1pt)

One point was counted for positive neonatal history in the following 4 categories:

- Feeding difficulties
- Respiratory distress

- Hypotonia
- Hyperbilirubinemia

One point was attributed even if the description lacked details.

Statistical analysis

We analyzed both total score and subscores. Separated analysis of the scores in the different categories (malformations including neuroanatomical anomalies, epilepsy, psychiatry, development delay, endocrinology, abnormal food behavior and neonatal complications) were performed. Statistical calculations and graphics were built on the computer program « R ». The total score had a two-tailed Student T-test to compare males and females. Each point we processed with Fisher's exact tests between males and females populations. Binomial test were run on population distribution between males and females. Fisher's test was also used to compare the rate of categorical diagnoses or minor malformations (not included in the score) between males and females.

Results

Gender stratification in BP1-3 and BP2-3 ascertainment

As previously reported there is an excess of males referred to the clinic for a neurodevelopmental disorder (NDs) (35). For deletion probands, there are close to twice as many males (n = 67) than females (n = 37) (p = 0.0042 ; Table 1). This difference comes from BP2-BP3 alone: males n = 60 and females n = 30, bias that is essentially driven by probands ascertained for NDs where males (n = 61) are close to two times more prevalent than females (n = 31) (p = 0.0073 ; Figure 2). Contrastingly, in deletion carriers not ascertained for NDs (general population + relatives), we observe a trend suggesting an excess of females (females n = 26 and males n = 16) (p = 0.19, binomial test).

We did not detect the same trends among duplication probands (males n = 30 and females n = 29). ND is more or less balanced between males and females (19 and 21 respectively) (Figure 2). ND stays the main cause of ascertainment in duplication probands (40/59 probands) but significant differences in gender distribution could not be demonstrated in this group. ND doesn't drive as clearly the type of ascertainment in the duplication probands, since a higher proportion of probands are ascertained from general population (19/59 probands) than in deletion probands (12/104 probands).

In BP2-BP3 proband's relatives, which represent our asymptomatic carriers, we see a trend towards an increased prevalence of females (p = 0.075, binomial test) in deletion (Figure 1). This could support the excess maternal transmission discussed in the introduction.

Anthropometry

BMI in BP2-3 rearrangements

We investigated the interaction between gender and gene dosage effects on BMI : (31) (Figure 3)

- Females: 1.5 z-score points between deletions and duplications (p = 0.003) (lm)
- Males: 3 z-score points between deletions and duplications (p = 4.93e-11) (lm)

There is no main effect of gender on BMI but as shown above, there is a significant interaction of gender with gene dosage. The effect of gene dosage is larger in males than in females (ANOVA). Among deletion patients there even is a significant difference between males and females (t.test)

Other anthropometric measures

We observed no gender effects for any of the other anthropometric measures.
The gene dosage effect for BP2-3 Head Circumference (31; Figure 4) in males was 2.4 z-score points between deletions and duplications (p = 3.41e-06). Females of the same group did not have such a trend.

Total clinical score

We compared the total clinical score in carriers of the deletion or the duplication probands and compared females and males total clinical score (Figure 5). No significant results were found. Both deletion and duplication have an average score of 2pts and there is no significant difference between females and males total score.
We then explored the individual following categories (Figure 6).

Psychiatric score in BP1-3 and BP2-3

Among all deletion and duplication probands, psychiatric disorders are more frequent in males compared to females (OR: 2.23 ; p = 0.016). This is also true for duplications carriers (OR: 3.26 ; p = 0.037) but the increase is not significant in deletions carriers (OR: 1.71 ; p = 0.22). Deletion only have a significant effect when observing ASD traits with a higher prevalence of males compared to females (OR: 3.10, p = 0.037) which drives the trend for an increase psychiatric disorders in males for this group. (Figure 7, Table 2)

On the other hand, duplication probands, males seem to have a higher prevalence of psychiatric disorders than females with an average of 0.97 and 0.52 psychiatric points respectively, this difference is also observed on PB2-BP3 males and females with an average of 0.90 and 0.67 respectively. The same trend is especially seen in anxiety disorder were only males are represented (7/30 males for BP1-BP3 + BP2-BP3 and 6/22 males for BP2-BP3 probands alone) (Figure 7). Other than anxiety disorders in duplication probands with a significant male predominance (p = 0,010 for BP1-BP3 +

BP2-BP3 and p = 0.0047 for BP2-BP3 probands alone) there is no other psychiatric symptoms with significant results.

In BP1-BP3 CNVs alone, 10/15 males have a psychiatric diagnosis and only one female out of eight have the same impairment (OR: 12.34 ; p = 0.027).

Malformations score in BP1-3 and BP2-3

Females present more malformations (including neuroanatomical anomalies) than males in all probands (deletions and duplications) (OR: 2.24 ; p = 0.048 ; Table 3). This is mostly driven by the deletion group (OR: 2.88 ; p = 0.056).

When looking at the different categories of malformation, a strong female signal comes from ENT malformations. In BP1-BP3 and BP2-BP3 probands, an odds ratio of 9.48 for ENT malformations in females is significant (p = 0.018 ; Table 3). This is driven by cleft lip or palate malformations (OR: 7.78 ; p = 0.040) and in duplication of the same break points females still have a trend for more cleft lip or palate malformations (p = 0.052) with 4/29 females with the malformation and 0/30 males. (Table 4)

Females also present more ophthalmological abnormalities: retinal anomalies (including retinal dystrophy blindness, central retinal changes and chorioretinal coloboma) are only present in BP2-BP3 for 3/58 females (p = 0.069). At the same break point, when looking at only duplication probands, strabismus is significantly more often in females (OR: 3.93 ; p = 0.027; Table 4).

Other medical issues

Males have a higher predominance for hypotonia in BP2-3 and BP1-3 CNV's probands with 23/97 males and 7/66 females (OR: 2.60, p = 0.040) and in repetitive otitis with only males positive (5/22) in BP2-3 of the duplication group (p = 0.032).

In duplication of BP1- BP3 and BP2-BP3 probands, epilepsy has a trend for females (9/66 females against 9/97 males) (OR: 4.53 ; p = 0.19 ; Table 5).

In BP2-BP3 probands there is nearly twice as many males (n = 25/72) than females (n = 10/58) with a neonatal complications (OR: 0.48 ; p = 0.079). This trend mainly comes from hypotonia described above. (Table 5)

Development delay

No significant difference between genders was found for development delay. IQ data was to low to make any analysis (only 4 females probands with IQ gatered and 19 males).

Discussion

As previously reported for other genomic variants, we observe an excess of male probands ascertained for NDs compared to females who carry the same 16p11.2 BP1-BP3 or BP2-BP3 deletion. Contrastingly, females ascertained as relatives are more likely than males to carry these CNVs. This has also been reported for other genomic variants. These sex biases are however not observed in the duplication group.

Systemic investigation of malformations, medical issues and psychiatric symptoms show that males carring a 16p11.2 BP1-3 or BP2-BP3 CNV are more likely than females to receive one or more psychiatric diagnosis. This result is significantly driven by duplication probands, especially for those with an anxiety disorder. Deletion male probands, have significantly higher rates of ASD diagnoses. Contrastingly, female carriers are more likely than males to have malformations. This result is significantly driven by ENT malformations, most markedly cleft-lip and palate. Females also revealed a trend towards an excess for other malformations or medical issues including retinal anomalies in deletion and duplication probands, refraction problem and abnormal palate in duplication probands and strabismus in deletion probands.

1. Ascertainment

The excess of non-proband females BP2-BP3 deletion carriers is consistent with the sex bias in fecundity reported in CNV carriers and patients with psychiatric disorders (9). The excess of maternally transmitted deleterious mutations is, in this case, concordant with the decreased fecundity more pronounced in males. Furthermore, we suggest a

potential social bias where the relative carriers may be more easily represented by mothers inclined to bring their child to the clinic and participate in research. While considering this hypothesis, there are still more males in ND ascertainment that suggest a higher penetrance of pathological phenotypes in males who carry a CNV.

As described in our results, the BP2-BP3 and BP1-BP3 duplication sample size is too restricted to determine a gender effect for our ND ascertainment. The analysis of clinical features from this group shows a trend similar to what is seen in deletion probands, with a higher rate of psychiatric diagnoses in males.

2. Clinical expressions in males

We interpret the increased rate of psychiatric diagnosis in males as one of the causal factors underlying the excess of male probands ascertained for NDs. Interestingly, in addition to ASD (for deletion carriers), anxiety and behavioral issues (for duplication carriers) are also more often observed in males. Males also show a higher penetrance for anthropometric features with a BMI difference of 3 z-score points between deletions and duplications (p =4.93e-11). The difference is twice that of females. In addition, males also show an average BMI higher than females when comparing to the deletion group.

3. Clinical expressions in females

Our results suggest that females present less psychiatric diagnoses, behavioral problems and anthropometric anomalies compared to males. Then which « female clinical expressions » bring female probands to the clinic? A global trend for a higher penetrance of malformations (especially ENT features such as cleft-lip or palate) is identified in females. In females with the duplication, we find more somatic anomalies like strabismus and retinal anomalies. Our understanding is that females are less ascertained because they present fewer psychiatric symptoms. It requires objective symptoms such as malformations or medical issues to refer girls to the clinic. The "female protective model" theory (6) says that high functioning females carry more often than males a higher CNV genetic burden. Combining our findings and this theory we could suspect that females are "protected" concerning neuropsychiatric symptoms and that they are

more likely to express "somatic phenotypes", either because they are not protected against it or because other genetic mutations induce it.

4. Conclusion and future perspectives

This study is concordant with « female protective model » but also suggests a « somatic female expression ». In order to know if it is one or both of the models, a number of new probands would need to be added to this database. An extension of these analyses to the BP4-BP5 region might be relevant to compare the results.

Limitations: Since clinical features in our database for BP1-BP3 and BP2-BP3 were only obtained through a form filled by patient practitioners, a one-on-one and systematic approach with the professionals of this research would be more precise.

Acknowledgments

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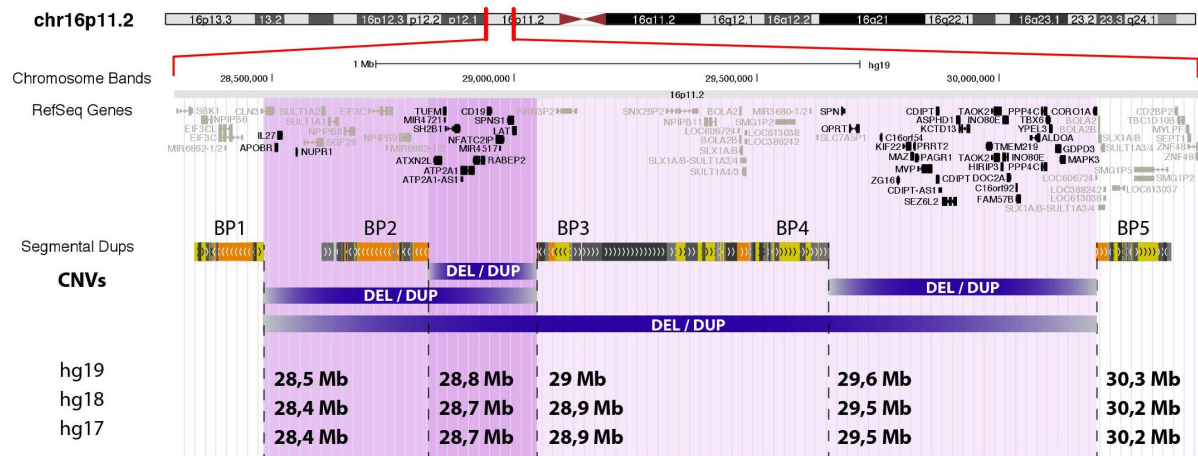
Figures and tables.

Figure 1: loci 16p11.2 and breakpoints © http://minds-genes.org

	Female probands	Male probands	Total probands	Binomial test 50/50 F vs M	Female relatives	Males relative	Total relatives	Binomial test 50/50 F vs M
DUP BP 1/2-3	29	30	59	p = 1	6	5	11	p = 1
DEL BP 1/2-3	37	**67**	104	p = **0.0042**	20	10	30	p = 0.099
DUP BP2-3	28	22	50	p = 0.48	5	4	9	p = 1
DEL BP2-3	30	**60**	90	p = **0.0021**	18	8	26	p = 0.075
DUP BP1-3	1	**8**	9	p = **0.040**	1	1	2	p = 1
DEL BP1-3	7	7	14	p = 1	2	2	4	p = 1

Table 1 :Distribution of males (M) and females (F) in probands and relative who carry a CNV. p-values were computed using a binomial tests comparing to a 50/50 sex distribution. Each groups is determined by their break-points (BP) and the number of copies (duplication = DUP or deletion = DEL). Red = female, blue =males.
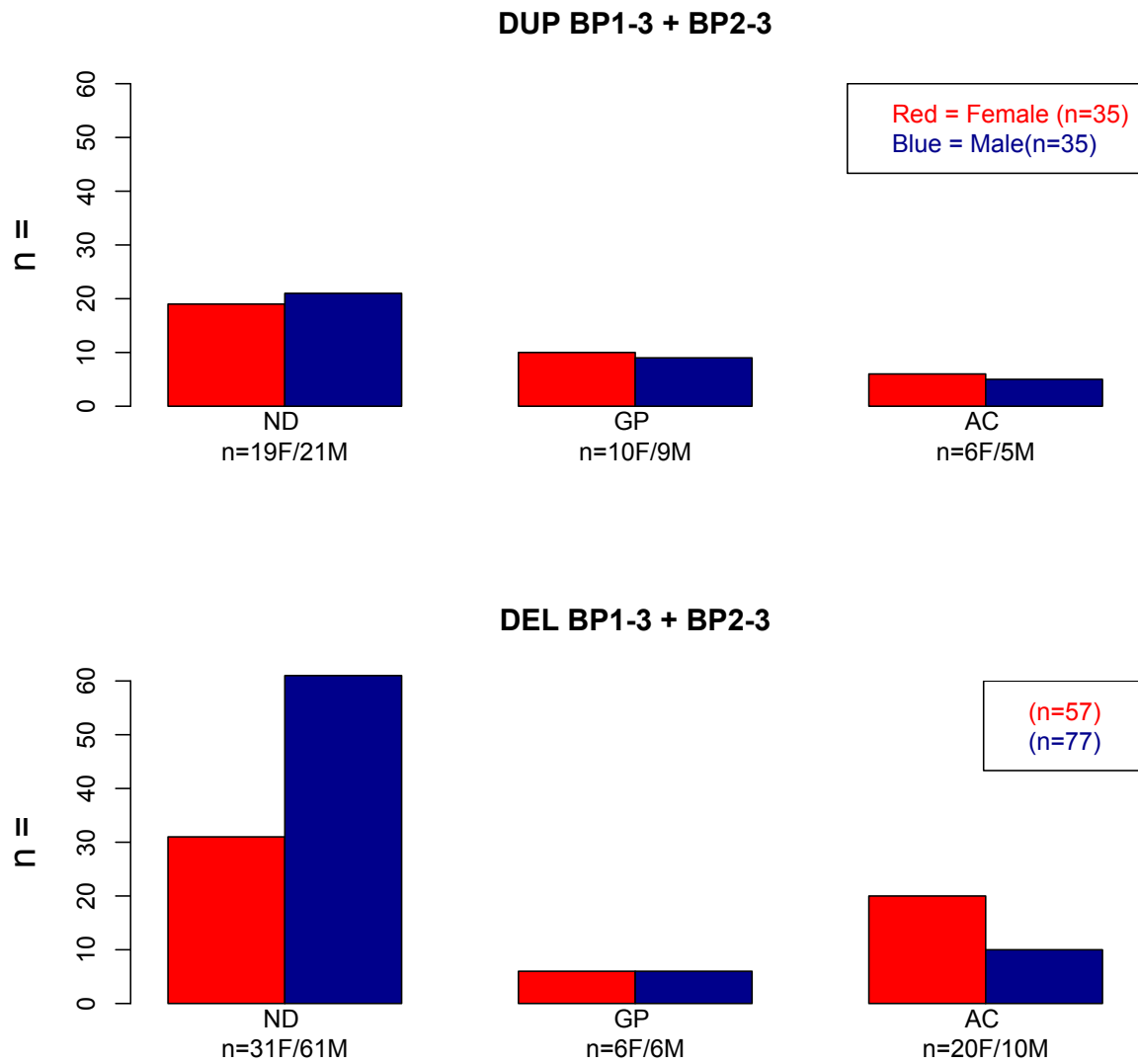
Figure 2 : Number (n) of female (red) and male (blue) proband carriers of BP2-3 CNVs ascertainmed as ND = neurodeveloppmental disorders, GP = general population and AC = asymptomatic relative carriers. DEL = deletion, DUP = duplication.
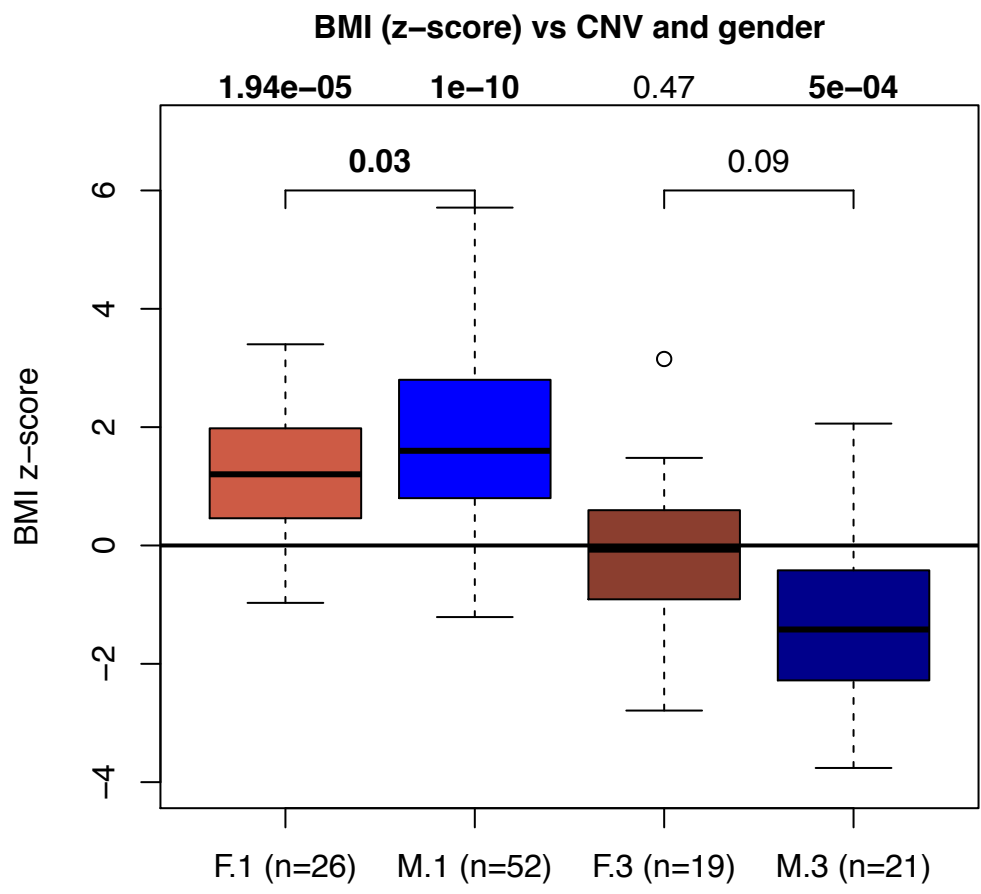
Figure 3 : Boxplots representing BMI z-score in females (F) and males (M) each for deletion (1), and duplication (3) BP2-3 carriers. Numbers of probands = n. P values above each boxplot correspond to the probability of the z score being equal to 0 (t-test).
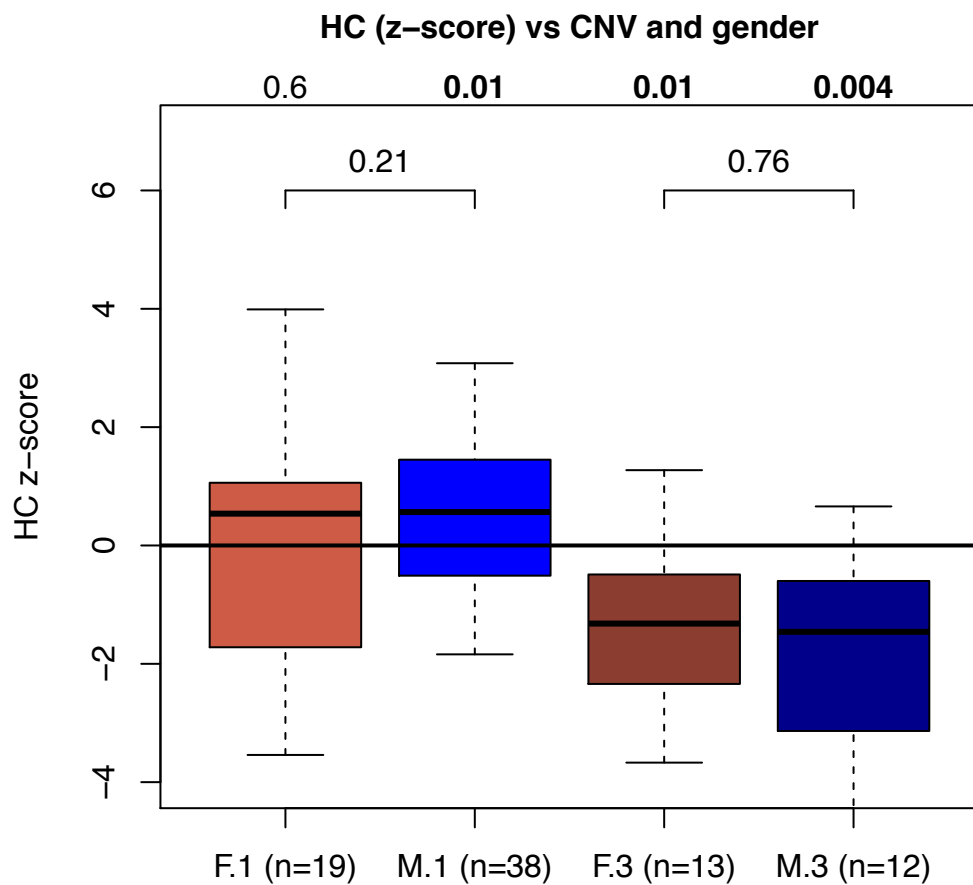
Figure 4 : Boxplots representing Head circumference (HC) z-score in females (F) and males (M) proband carriers of a BP2-3 deletion (1), or duplication (3). n=numbers of probands. P values above each boxplot correspond to the probability of the z score being equal to 0 (t-test).
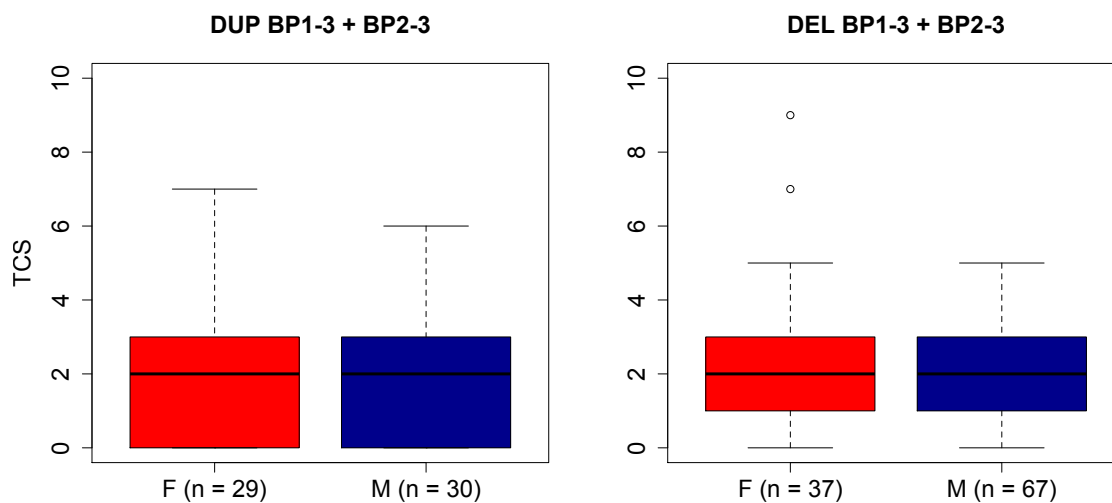

Figure 5 : Boxplots reprensenting the total clinical score (TCS) in female (F) versus male (M) probands carriers of a BP1-3 or BP2-3 CNVs (DEL = deletion, DUP = duplication). T-tests comparing the TCS between males and femles did not show any significant results.

DUP BP1-3 + BP2-3

Red = Female (n=29)
Blue = Male (n=30)

DEL BP1-3 + BP2-3

(n=37)
(n=67)

Figure 6 : Average score obtain (AvScore) for females (red) versus male (blue) deletion (DEL) and duplication (DUP) probands of BP1-3 and BP2-3 for the different categories described in the methodology : Malformations (MALFO), Neuroanatomical (MRI), Psychiatric disease (PSY), Developpment delay(DD), Anormal food behaviour (FOOD), Endocrinal anomalies (ENDO), Neonatal anomalies (NN) and the Total score (TOTAL).
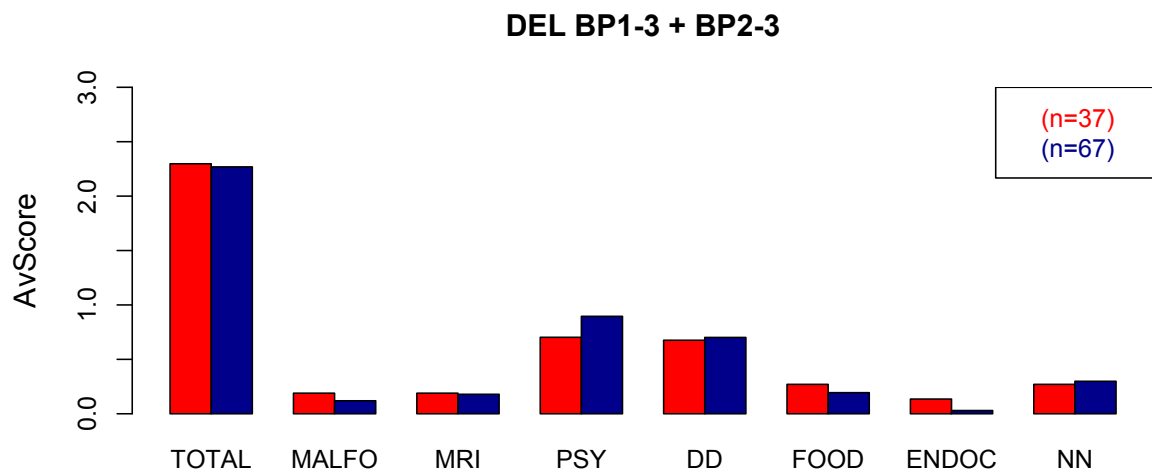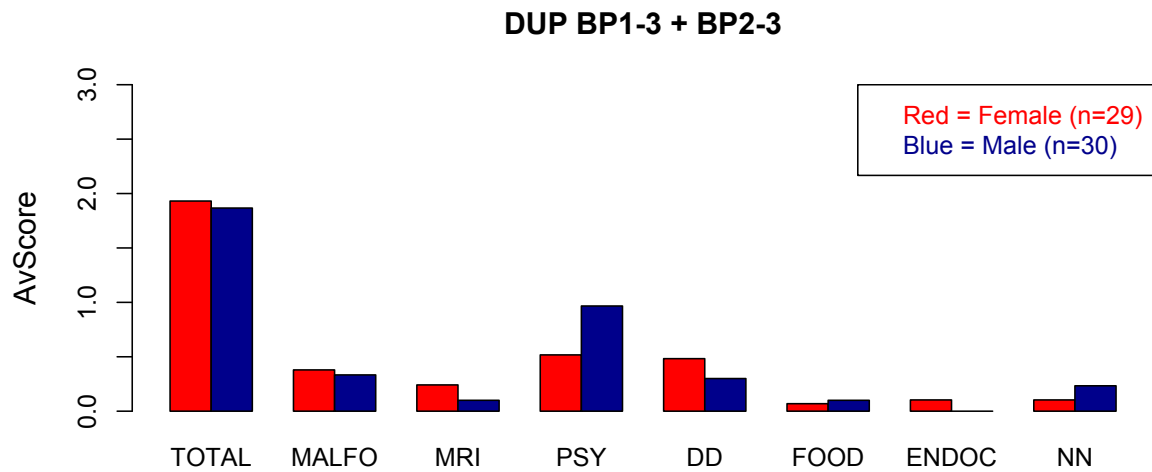
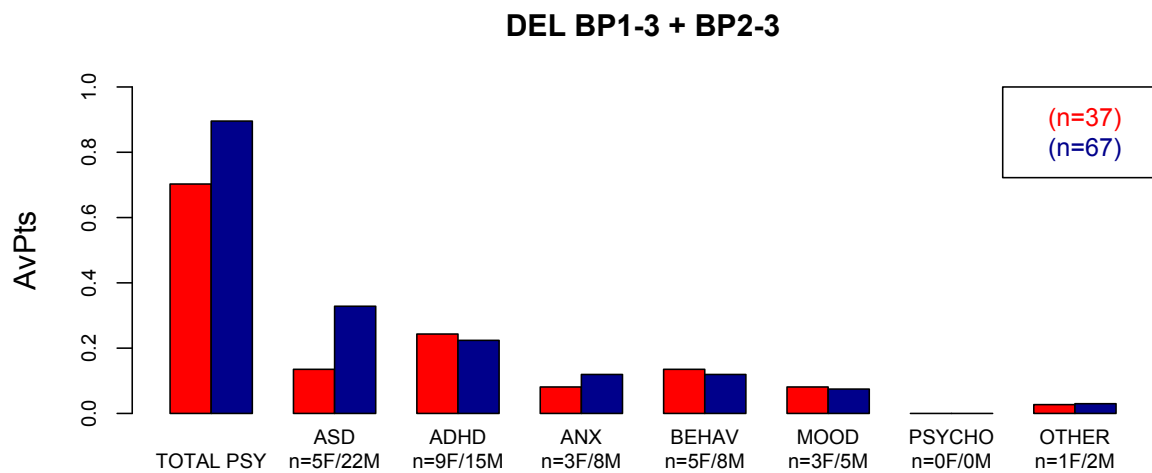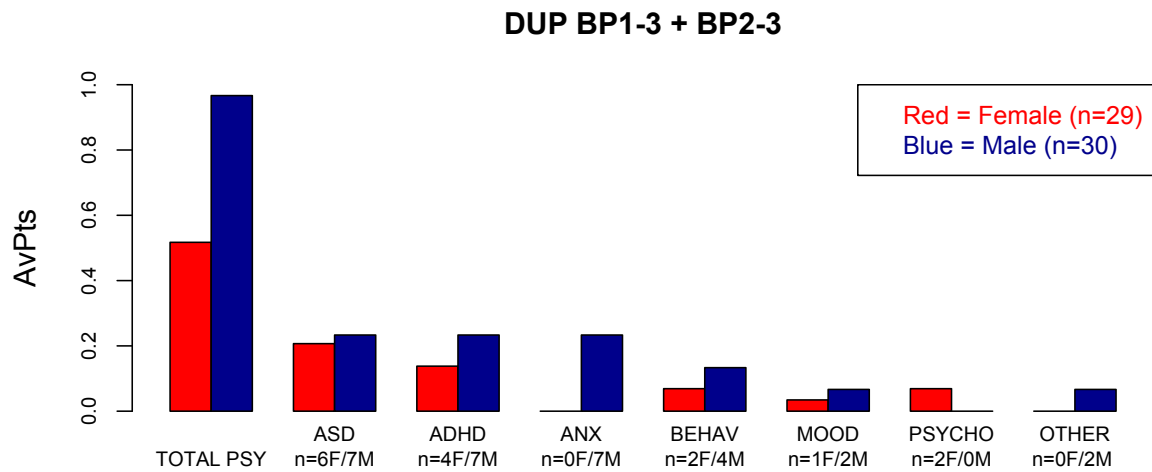**Figure 7 : Average points obtain (AvPts) for females (red) versus male (blue) deletion (DEL) and duplication (DUP) probands of BP1-3 and BP2-3 for the different psychiatric diagnosis described in the methodology : ASD, ADHD, Anxiety (ANX), Behevioural issues (BEHAV), Mood disorder (MOOD), Psychotic disorder (PSYCHO), OTHER and the Total psychiatric disorder score (TOTAL PSY). Statistic results on the next page.**

Fisher tests F vs M	≥1 psychiatic diagnosis	Anxiety disorder	ASD
BP1/2-3 DUP+DEL	OR : 2.23 (56/97M VS 25/66F) p = 0.017	OR : 3.81 (15/97M VS 3/66F) p = 0.040	OR : 2.12 (29/97M VS 11/66F) p = 0.064
DUP	OR : 3.26 (18/30M VS 9/29F) p = 0.037	OR : Inf (7/30M VS 0/29F) p = 0.010	-
DEL	-	-	OR : 3.10 (22/67M VS 5/37F) p = 0.037
BP2-3 DUP+DEL	-	OR : 3.12 (12/82M VS 3/58F) p = 0.098	OR : 1.98 (24/82M VS 10/58M) p = 0.11
DUP	OR : 2.98 (13/22M VS 9/28F) p = 0.086	OR : Inf (6/22M VS 0/28F) p = 0.0047	-
DEL	-	-	OR : 2.98 (19/60M VS 4/30F) p = 0.075
BP1-3 DUP+DEL	OR : 12.34 (10/15M VS 1/8F) p = 0.027	-	-
DUP	-	-	-
DEL	OR : 11.72 (5/7M VS 1/7F) p = 0.10	-	-

Table 2 : Table representig the results of Fisher exact test comparing the odds of males (M) with a psychiatric diagnosis, to female (F) . OR = odds ratio, DUP = duplication, DEL = deletion, p = p-value, dark-blue = OR of a significant males higher prevalence compared to females, light blue = OR of a trend for an exces of males compared to females.

Fisher tests F vs M	1 malfo (incl. neuroanat. data)	1 malfo	≥1 malfo (incl. neuroanat. data)	ENT malfo	Skelettal/ orthopedic malfo
BP1/2-3 **DUP+DEL**	-	-	**OR : 2.24 (19/66F VS 14/92M)** **p = 0.048**	**OR : 9.48 (6/66F VS 1/97M)** **p =0.018**	-
DUP	-	-	-	**OR : inf (5/29F VS 0/30M)** **p =0.024**	-
DEL	-	-	OR : 2.88 (10/37F VS 7/62M) p = 0.056	-	OR : 5.72 (3/37F VS 1/67M) p = 0.13
BP2-3 **DUP+DEL**	-	-	-	**OR : 9.21 (6/58F VS 1/82M)** **p =0.020**	-
DUP	-	-	-	OR : inf (5/28F VS 0/22M) p = 0.059	-
DEL	-	-	-	-	-
BP1-3 **DUP+DEL**	**OR : inf (4/8F VS 0/15M)** **p = 0.0079**	OR : inf (2/8F VS 0/15M) p = 0.11	**OR : 12.11 (4/4F VS 1/14M)** **p = 0.033**	-	-
DUP	OR : inf (1/1F VS 0/8M) p = 0.11	-	-	-	-
DEL	-	-	-	-	-

Table 3 : Table representig the results several significant Fisher exact test comparing the odds of female (F) malformations, used as a point in our score, to males (M). OR = odds ratio, DUP = duplication, DEL = deletion, p = p-value, ≥1Malfo = ≥1 malformation(s) including or not the neuroanatomical malformation detected on MRI or CT, red = OR of a significant females higher prevalence compared to males, pink = OR of a trend for an exces of females compared to males.

Fisher tests F vs M	OPHTALMO Strabismus	Retinal problem	Refraction problem	ENT Cleft lip/palate	Anormal palate	ORTHO Pectus excavatum	Scoliosis
BP1/2-3 DUP+DEL	-	OR : inf (3/66F VS 0/97M) p = 0.065	-	**OR : 7.78 (5/66F VS 1/97M) p = 0.040**	-	-	-
DUP	-	OR : inf (3/29F VS 0/30M) p- = 0.11	OR : inf (3/29F VS 0/30M) p= 0.11	OR : inf (4/29F VS 0/30M) p = 0.052	OR:4.53 (4/29F VS 1/30M) p = 0.19	OR : Inf (4/30M VS 0/29F) p = 0.11	-
DEL	**OR : 3.93 (9/37F VS 5/67M) p = 0.032**	-	-	-	-	-	-
BP2-3 DUP+DEL	-	OR : inf (3/58F VS 0/82M) p =0.069	-	OR : 7.54 (5/58F VS 1/82M) p = 0.082	OR : 3.74 (5/58F VS 2/82M) p = 0.13	-	-
DUP	-	-	-	OR : inf (4/28F VS 0/22M) p = 0.12	OR : inf (4/28F VS 0/22M) p = 0.12	OR : Inf (3/22M VS 0/28F) p = 0.079	OR : 5.80 (4/22M VS 1/28F) p = 0.15
DEL	**OR : 3.93 (8/30F VS 5/60M) p = 0.027**	-	-	-	-	-	-
BP1-3 DUP+DEL	-	-	OR : inf (2/8F VS 0/15M) p = 0.11	-	-	-	-
DUP	-	-	OR : inf (1/1F VS 0/8M) p = 0.11	-	-	-	-
DEL	-	-	-	-	-	-	-

Table 4 : Table representig the results of Fisher exact test comparing the odds of female (F) with specific malformations or medical diagnosis to males (M). OR = odds ratio, DUP = duplication, DEL = deletion, p = p-value, red = OR of a significant females higher prevalence compared to males, pink = OR of a trend for an exces of females compared to males, light blue = OR of a trend for an exces of males compared to females.

Fisher tests F vs M	EPILEPSY	ENDOCRINE ANOMALY	GH deficiency	NEONATAL COMPLICATION	HYPOTONIA	REPET. OTITIS
BP1/2-3 DUP+DEL	-	-	OR : inf (3/66F VS 0/97M) p = 0.065	-	**OR : 2.60 (23/97M VS 7/66F) p = 0.040**	-
DUP	OR : 4.53 (4/29F VS 1/30M) p = 0.19	-	-	-	-	OR : Inf (4/30M VS 0/29F) p= 0.11
DEL	-	-	-	-	-	-
BP2-3 DUP+DEL	-	-	-	OR : 2.09 (25/82M VS 10/58F) p = 0.079	**OR : 2.60 (19/82M VS 6/58F) p = 0.07**	-
DUP	-	-	-	-	-	**OR : Inf (4/22M VS 0/28F) p= 0.032**
DEL	-	-	-	-	-	-
BP1-3 DUP+DEL	-	OR: Inf (2/8F VS 0/15M) p = 0.11	-	-	-	-
DUP	-	OR: Inf (1/1F VS 0/8M) p = 0.11	-	-	-	-
DEL	-	-	-	-	-	-

Table 5 : Table representig the results of several significant Fisher exact test comparing the odds of female (F) other medical diagnosis, to males (M). OR = odds ratio, DUP = duplication, DEL = deletion, p = p-value, pink = OR of a trend for an exces of females compared to males, light blue = OR of a trend for an exces of males compared to females, dark-blue = OR of a significant males higher prevalence compared to females.

Fisher tests F vs M	Development delay	Speech sound disorder	Learning difficulties	Lecture difficulties	
	Probands with ASD	Probands with ASD	Probands not ASD	All probands	Probands not ASD
BP1/2-3 DUP+DEL	OR: 4.81 (27/29M VS 8/11F) p=0.12	-	OR: 6.61 (5/55F VS 1/68M) p=0.088	-	OR: 6.61 (5/55F VS 1/68M) p=0.088
DUP	OR: Inf (7/7M VS 3/6F) p=0.069	OR: Inf (4/7M VS 0/6F) p=0.070	-	-	-
DEL	-	-	OR: 7.94 (5/32F VS 1/45M) p=0.076	OR: 4.99 (5/37M VS 2/67M) p=0.094	OR: 7.94 (5/32F VS 1/45M) p=0.076
BP2-3 DUP+DEL	OR: 9.07 (23/24M VS 7/10F) p=0.067	-	-	-	-
DUP	-	OR: Inf (3/5M VS 0/6F) p=0.061	-	-	-
DEL	-	-	OR:7.061 (4/26F VS 1/41M) p=0.070	OR: 4.38 (4/30F VS 2/60M) p=0.093	OR: 7.061 (4/26F VS 1/41M) p=0.070
BP1-3 DUP+DEL	-	-	-	-	-
DUP	-	-	-	-	-
DEL	-	-	-	-	-

Table 6 : Table representig the results of several trend revieled by Fisher exact test comparing the odds of female (F) development delay (DD) to males (M). OR = odds ratio, DUP = duplication, DEL = deletion, p = p-value, pink = OR of a trend for an exces of females compared to males, light blue = OR of a trend for an exces of males compared to females.