a0001

The Molecular Genetics of Trisomy 18: Phenotype–Genotype Correlations

Angela Peron, *Department of Pediatrics, Division of Medical Genetics, University of Utah School of Medicine, Salt Lake City, Utah, USA*

John C Carey, *Department of Pediatrics, Division of Medical Genetics, University of Utah School of Medicine, Salt Lake City, Utah, USA*

Advanced article

Article Contents

Online posting date: 17th November 2014

The trisomy 18 syndrome can result from a full, mosaic, or partial trisomy 18. The main clinical findings of full trisomy 18 consist of prenatal and postnatal growth deficiency, characteristic facial features, clenched hands with overriding fingers and nail hypoplasia, short sternum, short hallux, major malformations, especially of the heart, and profound intellectual disability in the surviving older children. The phenotype of partial trisomy 18 is extremely variable. The aim of this article is to systematically review the scientific literature on patients with partial trisomy 18 in order to identify regions of chromosome 18 that may be responsible for the specific clinical features of the trisomy 18 syndrome. We confirmed that trisomy of the short arm of chromosome 18 does not seem to cause the major features. However, we found candidate regions on the long arm of chromosome 18 for some of the characteristic clinical features, and a thus a phenotypic map is proposed. Our findings confirm the hypothesis that single critical regions/candidate genes are likely to be responsible for specific characteristics of the syndrome, while a single critical region for the whole Edwards syndrome phenotype is unlikely to exist.

s0001

Introduction

p0001

The trisomy 18 syndrome, also known as Edwards syndrome, is caused by the presence of a supernumerary chromosome 18. The condition was recognised as a specific syndrome by Edwards *et al*. (1960) and Smith *et al*. (1960) Trisomy 18 represents the second most common autosomal trisomy after trisomy 21 (Down syndrome), with a live birth prevalence ranging from 1/3600 to 1/10 000. The overall frequency is higher due to pregnancy losses and terminations (Cereda and Carey, 2012). There is a female to male prevalence (F:M = 3:1), and liveborn females have a better survival compared to males (Jones *et al*., 2013). Neonatal and infant mortality is high, with the majority of patients dying during labour (38.5%) (Yamanaka *et al*., 2006) or by the first year of age, with less than 10% surviving beyond their first birthday (Carey, 2010; Cereda and Carey, 2012). **See also**: Trisomy

p0002

With respect to aetiology, Edwards syndrome can result from a full (94% of cases), mosaic (<5%), or partial (approximately 2%) trisomy 18 (Carey, 2010). In the full trisomy every cell contains three complete copies of chromosome 18. In mosaic trisomy two different cell lines coexist: one with three copies of chromosome 18 and one normal cell line, present in different percentages in different tissues. In partial trisomy only parts of the long and/or short arms of chromosome 18 are duplicated and thus present in three copies.

p0003

The main clinical findings of full trisomy 18 are: prenatal and postnatal growth deficiency, characteristic facial features (dolichocephaly/prominent occiput, short palpebral fissures, small mouth, micrognathia, external anomalies of the ears and redundant skin at the back of the neck), clenched hands with overriding fingers and nail hypoplasia, short sternum, short hallux and major malformations (cardiac, genitourinary, gastrointestinal, feet and CNS). Those who survive infancy have significant motor and intellectual disability (ID). We propose that the constellation of these features taken together as a whole comprises the Edwards syndrome phenotype (Carey, 2013). The phenotype of individuals with mosaic trisomy 18 is extremely variable, ranging from complete trisomy 18 phenotype to apparently normal adults. The phenotypes of individuals with partial trisomies are highly variable, depending on the duplicated regions and their extent. **See also**: Chromosomal Syndromes and Genetic Disease

p0004

In 2005 the sequence and gene annotation of human chromosome 18 was published (Nusbaum *et al*., 2005). Chromosome 18 represents approximatively 2.7% of the human genome, and has the lowest gene density of any human chromosome, having 337 genes with an average of 4.4 genes per Megabase and several gene deserts

eLS subject area: Genetics & Disease

How to cite:
Peron, Angela; and Carey, John C (November 2014) The Molecular Genetics of Trisomy 18: Phenotype–Genotype Correlations. In: eLS. John Wiley & Sons, Ltd: Chichester.
DOI: 10.1002/9780470015902.a0025246

representing 38% of the entire chromosome (Nusbaum *et al*., 2005). 337 genes is a relatively small number if compared to other chromosomes: this may explain why some individuals with trisomy 18 can survive through pregnancy and why early miscarriage does not occur commonly. **See also**: Chromosome 18

p0005 During the last 30 years, some attempts to determine the critical region of chromosome 18 that results in the classical Edwards syndrome phenotype have been proposed (Wilson, 1993; Boghosian-Sell *et al*., 1994), but no consensus has been reached thus far. Generally speaking, full trisomies are caused by the presence of a whole extra chromosome, but subsets of specific clinical features can be caused by the duplications of small regions of the chromosome (Korenberg *et al*., 1994). As suggested for Down syndrome, individuals with a condition caused by duplications of only part of the chromosome provide the human models. This method has been useful in finding genes for congenital heart defects in Down syndrome and in linking copy number variations (CNVs) to human diseases (Korenberg *et al*., 1994; Korbel *et al*., 2009). Ideally, this approach applies also to trisomy 18. Consequently, as happened for Down syndrome, the concept of a critical region for the syndrome (meaning a specific region that is sufficient to cause the entire phenotype) has recently changed into the concept of critical regions/single candidate genes responsible for specific clinical features (Lyle *et al*., 2009). As previously stated by Epstein *et al*. (1991) for Down syndrome, the distinctive phenotypic features are likely to be due to imbalance of one or very few genes in a distinct region and should therefore be mappable. Cases of partial trisomy 18 are potentially useful in linking the single features with the specific regions of chromosome 18, but unfortunately they represent only 2% of all trisomy cases. Moreover, some are not isolated duplications, having instead an accompanying deletion on the same or on another chromosome as a result of an unbalanced inversion or translocation, and thus representing a confounding factor (Tucker *et al*., 2007). In addition, most reports of even partial trisomy 18 are based on standard cytogenetic studies, and only the few most recent ones have molecular characterisation of the duplicated regions. However, thanks to the newly available molecular technologies such as chromosomal microarray (array-CGH or SNP-array), physicians and scientists have been able to better characterise partial duplications. Although still a relatively small number, new patients with partial duplications of chromosome 18 have been reported in recent years in the scientific literature, and even more are expected to be found. Thus, a new attempt at inferring phenotype–genotype correlations can be initiated. **See also**: Down Syndrome; Microarrays in Disease Diagnosis and Prognosis

p0006 Understanding the regions of chromosome 18 responsible for the single features of Edwards syndrome would help elucidate the pathogenic mechanisms, but it would have an even greater clinical value: being able to make a proper genotype–phenotype correlation could help in the clinical management of these patients, focusing the follow up and the health supervision on selected features and avoiding unnecessary exams or procedures. Eventually, that would possibly lead to a better care and better quality of life for the individuals with the condition.

p0007 The aim of this article is to systematically review the most relevant scientific literature in order to identify regions of chromosome 18 that may be responsible for certain clinical features of trisomy 18 ('phenotype–genotype correlation' or 'phenotypic mapping'). Reports of partial short arm (18p) and long arm (18q) duplications present in the scientific literature since the late 1970s were reviewed and tabulated to include the individual clinical features of trisomy 18, with a specific attention to the cases with a molecular characterisation of the partial duplications (**Table 1**). We focused our review on patients with pure partial duplications or duplications resulting from a translocation between chromosome 18 and the short arm of an acrocentric chromosome (13, 14, 15, 21 and 22), which are known to contain only heterochromatin and are thus not expected to affect the phenotype. The mosaic patients were excluded. A further comment is warranted for the cases with a partial duplication of chromosome 18 and a deletion in the same or in other chromosomes: we decided to include them in the review too, after excluding the clinical features that could be associated with the deletions and could potentially modify the phenotype. Since the majority of patients were characterised by conventional karyotype and many of them had inadequate band resolution, we decided to include the largest duplications possible (especially when sub-bands were not available) rather than the smallest ones, in order not to miss potential candidate regions. This is a limitation of this study, and we are aware that this approach might be too broad in scope, but we chose to be inclusive rather than exclusive. Although biased, we decided to use this approach because the aim of this study was to attempt a tentative and current phenotypic map of chromosome 18 in hope that reports of new patients characterised by microarray will narrow the proposed critical regions for a phenotype.

p0008 When trying to create a phenotype–genotype correlation, one could use two different approaches (Epstein *et al*., 1991): the first consists of analysing the partial duplications and reporting what characteristics the patients have, regardless of the features of trisomy 18; the second one is to pick each single clinical feature of trisomy 18 and look for what type of duplications the patients with that specific feature have. We chose to use the first approach for the review of 18p duplications and the second approach for the review of 18q duplications.

General Knowledge/Previous Approaches

s0002

p0009 In the 1980s Turleau *et al*. (1980) proposed that triplication of 18p had little influence in the trisomy 18 phenotype, AU:2

while interaction of the triplicated segments 18q11–q13 and 18q22–qter was critical. However, Matsuoka *et al.* (1981) suggested the role of region 18q21, while Mücke *et al.* (1982) inferred that the critical region should be proximal to 18q12.2. On the other hand, region 18q11 was subsequently excluded by Mewar *et al.* (1993) as a candidate critical region following a molecular analysis of patients with a partial duplication of chromosome 18. As reported by Wilson *et al.* (1990), patients trisomic for all the 18p and part of the 18q have a progressively more severe phenotype as the trisomic portion extends down the chromosome (towards the terminus of the long arm), supporting the hypothesis that the short arm does not play much of a role in the phenotype. However, Boghosian-Sell *et al.* (1994) hypothesised that there is not a single region on the long arm of chromosome 18 that is sufficient to produce the Edwards syndrome phenotype, but trisomy for at least two regions is necessary to elicit the full phenotype. They identified the two critical regions as 18q12.1–18q21.2 and 18q22.3–qter. Notably the two patients reported by Boghosian-Sell *et al.* have most but not all the features seen in older children with full trisomy 18, and both survived the first year of life. These cases suggest that at least for the predisposition to high infant mortality in trisomy 18, there may be some critical genes on the 18p that play a role. Mewar *et al.* (1993) also described two patients with a pure partial duplication of the long arm of chromosome 18 who did not show the typical features of Edwards syndrome. The duplicated segments were 18q21.2–q22.2 and 18q12.12–q22.32, suggesting that these regions do not cause the core phenotype of Edwards syndrome. Interestingly, the two aforementioned patients and two other cases with 18q duplication resulting from unbalanced translocations involving other chromosomes have in common region 18q12.2–q22.2 duplicated, and they all present with growth retardation, developmental delays and seizures.

p0010 As the reader can observe, no definite consensus was reached in the past years. Therefore, let us analyse the scientific literature and the single regions of chromosome 18 with the more modern approach.

s0003 Partial Trisomy of the Short Arm (18p)

p0011 What is known and generally accepted is that the short arm does not contribute to the trisomy 18 phenotype.

p0012 Marical *et al.* (2007) provided a good review of all the cases with isolated 18p duplications. Rodríguez *et al.* (2007) described a male with pure trisomy 18p with an atrial septal defect, a club foot and normal psychomotor development; the trisomy was inherited from the mother who only showed mild cognitive impairment. Mabboux *et al.* (2007) reported a 13-year-old male with minor facial anomalies, bilateral cryptorchidism and moderate intellectual disability. Schramm *et al.* (2011) recently identified a patient with duplication of 18p11.21–q12.1 with anorectal malformation (ARM), patent ductus arteriosus (PDA) and normal intelligence, supporting the previous statement. Only about 15% of cases with full trisomy 18 present with an anorectal malformation, and this recent report suggests further studies in order to find out whether region 18p11.21–q12.1 could be implicated in the embryonic development of the anorectum. However, Bartels *et al.* (2011) speculated that the telomeric part of the short arm of chromosome 18 could contain a gene responsible for ARM, but this hypothesis has not been confirmed. We would suggest that distant regulation cannot be excluded in these cases.

p0013 Including the previously cited studies, which are the most recent ones, there are only 12 cases overall in the scientific literature with a pure trisomy of 18p, and all of them show various nonspecific minor anomalies and a mental development ranging from normal to moderate impairment (Taylor *et al.*, 1975; Takeda *et al.*, 1989; Wolff *et al.*, 1991; Moog *et al.*, 1994; Li *et al.*, 1998; Oner *et al.*, 2000). Furthermore, in some cases the duplication was inherited from a mildly affected mother, supporting the hypothesis that, although the number is small, 18p duplication is associated with a mild phenotype compatible with fertility, at least in females.

p0014 However, Hu *et al.* (2013) reported two cases of aortic coarctation in two foetuses with a duplication of 18pter–p11.21 and a deletion of 18q21.33–qter. Since they found two other patients with aortic coarctation and 18p aberrations in the DECIPHER database (http://decipher.sanger.ac.uk), they proposed that a gene in the short arm of chromosome 18 might be responsible for this congenital heart malformation, and hypothesised that the critical region for aortic coarctation may reside between breakpoints chr18:150 408–4 564 563, but found no candidate genes in that interval. No other cases have been reported so far. Notably the most common heart malformations observed in Edwards syndrome are septal defects, patent ductus arteriosus (PDA) and polyvalvular disease, while aortic coarctation does not seem to be typical of this condition.

p0015 Finally, Slavin *et al.* (2010) described a patient with 18p11.21–q11.2 duplication (due to a mosaic *de novo* ring18) and hemivertebrae and rib abnormalities with normal development and normal facial features, and analysed possible genes involved in skeletal formation and regulation.

p0016 In conclusion, trisomy of the short arm of chromosome 18 does not seem to cause any of the major features of Edwards syndrome. Further studies are needed to elucidate whether the short arm of chromosome 18 contains candidate genes for aortic coarctation and ARM.

Partial Trisomy of the Long Arm (18q) s0004

p0017 The long arm of chromosome 18 is thought to contain genes responsible for the main clinical features of Edwards syndrome. The most significant articles on partial 18q

duplications from late 1970s to nowadays were reviewed (**Table 1**) and an attempt to find candidate regions for the most common clinical features of the syndrome was made. The results are discussed below.

p0018 However, there are some exceptions. Henson *et al.* AU:3 (2010) reported three members of the same family (a stillborn, her half-sister and her mother) with an 18.35 Mb interstitial duplication of 18q21.32–q22.3 with a normal phenotype and apparently normal intelligence, and propose that this region be excluded from the critical regions of trisomy 18. Isidor *et al.* (2008) described a foetus with an interstitial 18q23 duplication of 450 Kb with a severe phenotype consisting of complex cortical malformations, facial anomalies and heart structural defects. The duplication was inherited from the healthy father. Although some of the clinical features are shared with patients with full trisomy 18 (agenesis of corpus callosum, cerebellar hypoplasia and heart septal defects), it is our opinion that the duplication inherited from the father cannot alone explain the complex phenotype, and decided therefore to exclude this patient from the review.

p0019 In order to establish a phenotype-genotype correlation, we analysed the single most common clinical features of Edwards syndrome and correlated them with duplications in the patients described in the scientific literature.

p0020 A phenotypic map of chromosome 18 based on the review of the literature is shown in **Figure 1**. The table summarises the reported cases used to propose the current map.

s0005 Growth delay and microcephaly

p0021 Concerning growth delay, the smallest duplicated region in common to most patients is 18q22.1 (**Table 1**). However, there are some patients with growth delay that share the duplicated 18pter–q12.2 region. Therefore, it is reasonable to posit that different regions and multiple genes on the chromosome could contribute to the same clinical feature.

p0022 With respect to microcephaly, we found that most patients share common duplicated regions in 18q12.2–q12.3 and 18q22.1–q22.3: again, different genes could be responsible for this feature.

s0006 Structural heart defects

p0023 The majority of patients with partial duplications showed structural heart defects, but we were not able to find a unique common duplicated region. The majority of cases had duplications that comprise regions 18q21.2 and 18q22.1–q22.2 (**Table 1**). However, other patients with congenital heart malformations that are not trisomic for the aforementioned regions shared a minimal common duplication in 18p11.21–18q11.2 (**Table 1**). Considering these patients and the ones described by Hu *et al.* (2013), we found that they all share region 18p11.21, and one could speculate that this may be another candidate region for heart defects. Taken together, these data support the hypothesis that multiple different regions could contain genes responsible for the heart malformations of Edwards syndrome, and a common candidate region for all patients is unlikely to exist.

Genitourinary malformations s0007

With respect to GU malformations, the two minimal duplicated regions in common to most patients with abnormal genitalia (cryptorchidism and hypotrophic/hypertrophic labia majora) are 18q12.2–q12.3 and 18q22.1–q22.2. Of note, most patients with partial duplications presented minor GU anomalies such as cryptorchidism and hypotrophic female genitalia: therefore, the critical region for major malformations such as horseshoe kidney might be located in a different part of chromosome 18. p0024

Gatrointestinal malformations s0008

Five patients with partial duplications of the long arm of chromosome 18 showed omphalocele/umbilical hernia, and they share a minimal common duplicated region in 18q21.31–q23, suggesting this may be the candidate region for this type of malformation (Neu *et al.*, 1976; Fryns *et al.*, 1978; Boghosian-Sell *et al.*, 1994; Mewar *et al.*, 1993). p0025

Characteristic facial and physical features s0009

By reviewing both the articles' content and the published photos, we analysed each typical facial dysmorphism, as well as the distinctive physical characteristics such as clenched hands with overriding fingers, and limb and sternum anomalies. Although we could apparently narrow down the critical regions for each feature to some bands of chromosome 18, we could not find a unique duplicated region shared by all the patients. Given the fact that sometimes the description of the facial anomalies may have been subjective and for some papers no complete information is available, we were only able to conclude that genes responsible for the facial features of Edwards syndrome are located in the long arm of chromosome 18. Interestingly, when we analysed each single characteristic per se, we noted that region 18q21.2 is very frequently duplicated in the majority of patients (**Table 1**). It would be interesting to study this region. p0026

Most patients with clenched hands and overriding fingers have duplications in 18q12.2 and in 18q22.1–q22.3, which could therefore be considered two candidate regions for this feature. However, no specific region was found for nail hypoplasia. With respect to short hallux and short sternum, there were only three patients showing the aforementioned skeletal anomalies, respectively, but they all shared a minimal duplicated region in 18q11.2–q21.33. Furthermore, three patients presented with radial aplasia/limb defects, and their minimal common duplicated region is 18q21.1–q22.3. If we consider short hallux, short sternum and radial aplasia all together as skeletal defects, we note that the patients all share a common duplicated region ranging from 18q21.1 to 18q21.33. Analysing only three p0027

patients at a time is a limitation of course, but that could be a starting point for finding candidate genes whose function is involved in skeletal formation.

s0010 ## Developmental delay/intellectual disability

p0028 Both Boghosian-Sell *et al*. (1994) and Mewar *et al*. (1993) agreed that severe 'mental retardation' may be associated with duplication of region 18q12.3–q21.1. However, we could not either confirm their hypothesis or find a candidate region for ID. This is not surprising though, if we acknowledge that developmental delay/intellectual disability could be the result of multiple genes and regions, as seen in most genetic diseases. In a complex syndrome like trisomy 18, it is more likely that many different regions and genes interact with each other to cause the severe intellectual phenotype.

s0011 ## Tumours

p0029 A specific mention should be made for tumours in Edwards syndrome. Hepatoblastoma and Wilms tumour are the two most common tumours associated with congenital anomalies, and they have been reported in patients with trisomy 18. Hepatoblastoma is a rare paediatric tumour with an incidence of 1.2–1.5 cases per million in the USA and Europe (Tan *et al*., 2013). There seems to be a significant association between hepatoblastoma and trisomy 18 (Kitanovski *et al*., 2009; Tan *et al*., 2013). Twelve patients with trisomy 18 and hepatoblastoma have been reported in the scientific literature thus far: all of them but one are females, possibly because the female:male ratio in trisomy 18 is skewed towards females and their longer survival. Among the patients diagnosed with a stage 1 hepatoblastoma and treated with surgery and chemotherapy, all but one were alive after more than 2 years after treatment. Since all the patients with this association had full trisomy 18 (9 patients) or mosaic trisomy 18 (3 patients) but none of them had a partial duplication of chromosome 18, it is not possible to infer a candidate region for the development of this hembriologic tumour.

p0030 Patients with trisomy 18 are thought to have a higher risk of developing also Wilms tumour. It is a cancer of the kidneys that typically occurs in children, and the survival rate for this type of cancer is quite high if appropriate treatment is performed. There are 10 patients with full trisomy 18 and Wilms tumour in the current scientific literature; no patients with a duplication of the short arm of this chromosome and Wilms tumour have been described so far. Starr *et al*. (2014) found a patient with this type of cancer and a large duplication of 55 Mb of the long arm of chromosome 18 involving region 18q11.2–q23, containing the proto-oncogene *BCL2*. Although the duplicated region is quite large and affects almost the entire long arm of chromosome 18, this recent observation helps narrow the critical region for Wilms tumour. The authors suggest that patients with duplications of 18p or of a region not included in their patient's aberration likely do not require surveillance for this type of tumour, while only that patients with larger 18q duplications could benefit from the sonographic surveillance.

p0031 The nonrandom association between trisomy 18 and both hepatoblastoma and Wilms tumours raises issues about the surveillance, anticipatory guidance and the extent of care. Because the numbers of cases are small and there are no epidemiologic studies, compelling data are not available to indicate whether or not serial abdominal ultrasound and measurement of serum AFP should be performed routinely on the patients in order to detect possible tumours early. However, Wilms tumour has been observed in a few children through abdominal sonographic screening (Carey, 2010) suggesting benefit. Since the issues surrounding treatment options of children with trisomy 18 are complex, the final decision regarding routine surveillance should be left to parents in consultation with their primary and specialty care providers.

Seizures

s0012

p0032 A manifestation that is recently emerging for trisomy 18 is epilepsy. Previous reports stated an incidence of epilepsy associated with trisomy 18 of 25–50%. A recent study reported an even higher incidence of 64% (Kumada *et al*., 2013) although this series likely contains some selection bias. The authors evaluated the types of seizures in 11 patients with this disease aged over 1 year, and found that the age of onset is usually during infancy or early childhood, and the most common type of seizures are complex partial seizures, spasms and tonic seizures: at least in half of the cases, epilepsy is not responsive to treatment. The authors evaluated only the patients with a full trisomy 18, so a genotype-phenotype correlation was not possible. However, Ceccarini *et al*. (2007) reported a family with three affected siblings carrying an interstitial tandem duplication of 18q21.31–18q22.2 inherited from a healthy mosaic carrier mother. The authors reviewed also nine cases of overlapping duplications, and half of the patients presented with seizures, suggesting a possible role of that region in generating abnormal epileptic activity. Recently, a new patient with a duplication of 18q12.2–q22.3 was reported (d'Orsi *et al*., 2012): he showed generalised tonic–clonic seizures, atonic drop attacks and eating-induced epileptic spams from age 25, and also had bilateral opercular dysplasia and corpus callosum hypoplasia.

p0033 In the old literature there are 11 additional patients reported to have seizures, but the type and onset of seizures are not always well characterised. Based on the past and current literature, we could find that the minimal critical region shared by all patients is 18q22.1–q22.2 (**Table 1**). With respect to seizure onset, patients with duplications are expected to develop seizures from infancy or early childhood (Mewar *et al*., 1993), although seizures can also start in adolescence or adulthood (Boghosian-Sell *et al*., 1994; d'Orsi *et al*., 2012). Therefore, parents should be instructed to pay attention for possible seizures, and some patients may benefit from early EEG studies.

s0013 Conclusions

p0034 A phenotypic map of Edwards syndrome is shown in **Figure 1**. By reviewing the past and current literature of patients with partial duplications of chromosome 18 we were able to find possible candidate regions for some of the characteristic clinical features of the syndrome. It is not clear whether those regions contain genes that are involved per se in the phenotype (= cause it directly) or contain regulatory elements for different regions on chromosome 18 or on other chromosomes (i.e. long distance regulation).

p0035 Our findings confirm the hypothesis that single critical regions/candidate genes are likely to be responsible for specific clinical features of the syndrome in an additive manner, while a unique critical region for the whole Edwards syndrome phenotype is unlikely to exist. The most valuable conclusion is that the trisomy 18 phenotype results from interaction of several chromosome 18 regions which may produce a quite different phenotype when duplicated in isolation.

p0036 In conclusion, data remain limited and sparse; our analysis, with its limitations, should be considered an attempt at a phenotype–genotype correlation for Edwards syndrome. More cases of partial trisomy 18 characterised by chromosomal microarray are needed to correlate regions with specific clinical features. The widespread of microarray technologies (SNP-arrays and array-CGH) and the use of next generation technologies will ideally help clarify our findings in the next few years.

p0037 Therefore, we encourage clinical reports of partial duplications of chromosome 18 in order to expand this current attempt of phenotype–genotype correlation and better address issues about surveillance, anticipatory guidance and follow up of these patients, in order to improve their quality of life.

References

Barber JC (2005) Directly transmitted unbalanced chromosome abnormalities and euchromatic variants. *Journal of Medical Genetics* **42**(8): 609–629.

Bartels E, Draaken M, Kazmierczak B *et al*. (2011) De novo partial trisomy 18p and partial monosomy 18q in a patient with anorectal malformation. *Cytogenetic Genome Research* **134**(3): 243–248.

Boghosian-Sell L, Mewar R, Harrison W *et al*. (1994) Molecular mapping of the Edwards syndrome phenotype to two noncontiguous regions on chromosome 18. *American Journal of Human Genetics* **55**(3): 476–483.

Carey JC (2010) Trisomy 18 and trisomy 13 syndromes. In: Cassidy SB and Allanson JE (eds) *Management of Genetic Syndromes*, 3rd edn, pp. 807–823. New York, NY: John Wiley & Sons.

Carey JC (2013) Trisomy 18 Mosaicism: A Model for the Study of Mosaicism**.** Presented at the David W Smith Workshop on Malformations and Morphogenesis, Quebec.

Ceccarini C, Sinibaldi L, Bernardini L *et al*. (2007) Duplication 18q21.31-q22.2. *American Journal of Medical Genetics Part A* **143**(4): 343–348.

Cereda A and Carey JC (2012) The trisomy 18 syndrome. AU:4 *Orphanet Journal of Rare Diseases* **7**: 81.

d'Orsi G, Pascarella MG, Pansini A *et al*. (2012) Partial trisomy 18q and epileptic spasms induced by eating associated with bilateral opercular dysplasia. *American Journal of Medical Genetics Part A* **161A**(5): 1194–1195.

Edwards JH, Harnden DG, Cameron AH, Crosse VM and Wolff OH (1960) A new trisomic syndrome. *Lancet* **1**: 787–790.

Epstein CJ, Korenberg JR, Annerén G *et al*. (1991) Protocols to establish genotype-phenotype correlations in Down syndrome. *American Journal of Human Genetics* **49**(1): 207–235.

Henson KE, Hines KA, Weaver DD *et al*. (2010) Duplication of 18q21.32-q22.3 identified in a stillborn and two relatives with minimal dysmorphic features. *American Journal of Medical Genetics Part A* **158A**(7): 1788–1792.

Hu H, Hao J, Yao H *et al*. (2013) Prenatal diagnosis of de novo partial trisomy 18p and partial monosomy 18q recurrent in a family with fatal aortic coarctation. *Gene* **517**(1): 132–136.

Isidor B, Winer N, Joubert M *et al*. (2008) Inherited 18q23 duplication in a fetus with multiple congenital anomalies. *European Journal of Medical Genetics* **51**(3): 231–238.

Jones KL, Jones MC and del Campo M (2013) *Trisomy 18 syndrome, in Smith's recognizable patterns of human malformation*, 7th edn, pp. 14–19. Philadelphia, PA: Elsevier Sounders.

Kitanovski L, Ovcak Z and Jazbec J (2009) Multifocal hepatoblastoma in a 6-month-old girl with trisomy 18: a case report. AU:5 *Journal of Medical Case Reports* **3**: 8319.

Korbel JO, Tirosh-Wagner T, Urban AE *et al*. (2009) The genetic architecture of Down syndrome phenotypes revealed by high-resolution analysis of human segmental trisomies. *Proceedings of the National Academy of Sciences of the United States of America* **106**(29): 12031–12036.

Korenberg JR, Chen XN, Schipper R *et al*. (1994) Down syndrome phenotypes: the consequences of chromosomal imbalance. *Proceedings of the National Academy of Sciences of the United States of America* **91**(11): 4997–5001.

Kumada T, Maihara T, Higuchi Y *et al*. (2013) Epilepsy in children with trisomy 18. *American Journal of Medical Genetics Part A* **161A**(4): 696–701.

Lee NC, Chang SP, Chang CS *et al*. (2009) Cryptic subtelomeric deletion plus inverted duplication at chromosome 18q in a fetus: molecular delineation by multicolor banding. *Prenatal Diagnosis* **29**(11): 1058–1060.

Li S, Tuck-Muller CM, Martínez JE *et al*. (1998) Prenatal detection of de novo duplication of the short arm of chromosome 18 confirmed by fluorescence in situ hybridization (FISH). *American Journal of Medical Genetics* **80**(5): 487–490.

Lyle R, Béna F, Gagos S *et al*. (2009) Genotype-phenotype correlations in Down syndrome identified by array CGH in 30 cases of partial trisomy and partial monosomy chromosome 21. *Europea Journal of Human Genetics* **17**(4): 454–466.

Mabboux P, Brisset S, Aboura A *et al*. (2007) Pure and complete trisomy 18p due to a supernumerary marker chromosome associated with moderate mental retardation. *American Journal of Medical Genetics* **143**(7): 727–733.

Marical H, Le Bris MJ, Douet-Guilbert N *et al*. (2007) 18p trisomy: a case of direct 18p duplication characterized by

molecular cytogenetic analysis. *American Journal of Medical Genetics Part A* **143A**(18): 2192–2195.

Mewar R, Kline AD, Harrison W *et al.* (1993) Clinical and molecular evaluation of four patients with partial duplications of the long arm of chromosome 18. *American Journal of Human Genetics* **53**(6): 1269–1278.

Moog U, Engelen JJ, de Die-Smulders CE *et al.* (1994) Partial trisomy of the short arm of chromosome 18 due to inversion duplication and direct duplication. *Clinical Genetics* **46**(6): 423–429.

Nguyen-Minh S, Drossel K, Horn D *et al.* (2013) Combined deletion 18q22.2 and duplication/triplication 18q22.1 causes microcephaly, mental retardation and leukencephalopathy. *Gene* **523**(1): 92–98.

Nusbaum C, Zody MC, Borowsky ML *et al.* (2005) DNA sequence and analysis of human chromosome 18. *Nature* **437**(7058): 551–555.

Oner G, Jauch A, Eggermann T *et al.* (2000) Mosaic rearrangement of chromosome 18: characterization by FISH mapping and DNA studies shows trisomy 18p and monosomy 18p both of paternal origin. *American Journal of Medical Genetics* **92**(2): 101–106.

Rodríguez L, Liehr T, Mrasek K *et al.* (2007) Small supernumerary chromosome marker generating complete and pure trisomy 18p, characterized by molecular cytogenetic techniques and review. *American Journal of Medical Genetics Part A* **143A**(22): 2727–2732.

Schramm C, Draaken M, Bartels E *et al.* (2011) De novo duplication of 18p11.21–18q12.1 in a female with anorectal malformation. *American Journal of Medical Genetics Part A* **155A**(2): 445–449.

Smith DW, Patau K, Therman E and Inhorn SL (1960) A new autosomal trisomy syndrome: multiple congenital anomalies caused by an extra chromosome. *Journal of Pediatrics* **57**: 338–345.

Starr LJ, Sanmann JN, Olney AH *et al.* (2014) Occurrence of nephroblastomatosis with dup(18)(q11.2–q23) implicates trisomy 18 tumor screening protocol in selected patients with 18q duplications. *American Journal of Medical Genetics Part A* **164A**(4): 1079–1082.

Takeda K, Okamura T and Hasegawa T (1989) Sibs with tetrasomy 18p born to a mother with trisomy 18p. *Journal of Medical Genetics* **26**(3): 195–197.

Tan ZH, Lai A, Chen, CK, Chang KT and Tan AM (2013) Association of trisomy 18 with hepatoblastoma and its implications. *European Journal of Pediatrics* 2013 Aug 23. (Epub ahead of print)

AU:6

Taylor KM, Wolfinger HL, Brown MG and Chadwick DL (1975) Origin of a small metacentric chromosome: familial and cytogenic evidence. *Clinical Genetics* **8**(5): 364–369.

Tucker ME, Garringer HJ and Weaver DD (2007) Phenotypic spectrum of mosaic trisomy 18: two new patients, a literature review, and counseling issues. *American Journal of Medical Genetics Part A* **143**(5): 505–517.

Wilson GN (1993) Karyotype/phenotype correlation: Prospects and problems illustrated by trisomy 18. In: *The Phenotypic Mapping of Down Syndrome and Other Aneuploidy Conditions*, pp. 157–173. New York, NY: Wiley-Liss.

AU:11

Wilson GN, Heller KB, Elterman RD and Schneider NR (1990) Partial trisomy 18 with minimal anomalies: lack of correspondence between phenotypic manifestations and triplicated loci along chromosome 18. *American Journal of Medical Genetics* **36**(4): 506–510.

Wolff DJ, Raffel LJ, Ferré MM and Schwartz S (1991) Prenatal ascertainment of an inherited dup(18p) associated with an apparently normal phenotype. *American Journal of Medical Genetics* **41**(3): 319–321.

Yamanaka M, Setoyama T, Igarashi Y *et al.* (2006) Pregnancy outcome of fetuses with trisomy 18 identified by prenatal sonography and chromosomal analysis in a perinatal center. *American Journal of Medical Genetics Part A* **140**(11): 177–1182. Erratum in: *American Journal of Medical Genetics Part A* 2006 Aug 15;**140**(16): 1796.

Further Reading

Allanson J, Hennekam RC, Carey JC andBisecker LG (2009) The elements of morpholgy. *American Journal of Medical Genetics Part A* **149A**: 1–127.

Epstein CJ (2007) *The Consequences of Chromosome Imbalance: Principles Mechanisms and Models*. Cambridge University Press.

AU:7

Gardner RJ, Sunderland GR and Shaffer LG (2012) *Chromosome Abnormalities and Genetic Counseling*, 4th edn. Oxford: Oxford University Press.

Jorde LB, Carey JC and Bamshad MB (2010) *Medical Genetics*. Mosby/Elsevier.

AU:8

Schinzel A (2001) *Catalogue of Unbalanced Chromosome Aberrations in Man*. Berlin: Walter de Gruyter.

Article Title: The Molecular Genetics of Trisomy 18: Phenotype–Genotype Correlations

Article ID: A0025246

Article doi: 10.1002/9780470015902.a0025246

Version: 1

Previous version(s): None

Article type: Standard

Readership level: Advanced

Top level subject categories: Genetics & Disease

Keywords: trisomy 18 # Edwards syndrome # genotype–phenotype correlation # phenotypic map # 18p duplication # 18q duplication # intellectual disability

Key Concepts:

- The phenotype of human chromosomal syndromes is comprised of the individual component manifestations of the condition.
- Using case descriptions of patients with partial trisomy of a segment of a chromosome, an investigator can potentially map the well-defined and more specific phenotypic findings to a region of the chromosome. Narrowing a region allows for review of the known genes in the region and for hypothesising the causative gene(s) for the phenotype.
- The certainty in inferring a causative region or individual gene for a component manifestation depends on the specificity and consistency of occurrence of the individual feature.
- Correlations of phenotypes with genotypes can lead to detection of candidate genes which provide insight into disease mechanisms and ideally into the development of strategies for therapeutic intervention and prevention.
- The findings in this paper confirm the hypothesis that single critical regions/candidate genes are likely to be responsible for specific characteristics of the syndrome, while a single critical region for the whole Edwards syndrome phenotype is unlikely to exist.

Glossary:

Genotype#The genetic constitution of an individual, at one or more gene loci.

Phenotype#The appearance of the organism, resulting from the interaction of its genetic constitution with the environment.

Microarray#A high-density miniaturised array of oligonucleotides spotted onto a glass slide. Genomic arrays hybridise DNA to identify cryptic deletions and duplications.

AU:9 AU:10

Author(s) and affiliation(s): Peron, Angela / Department of Pediatrics, Division of Medical Genetics, University of Utah School of Medicine, Salt Lake City, Utah, USA; Carey, John C / Department of Pediatrics, Division of Medical Genetics, University of Utah School of Medicine, Salt Lake City, Utah, USA

t0001 **Table 1** Clinical features of the cases of partial trisomy 18 present in the scientific literature

Clinical features	Jenkins *et al.* (1974)	Neu *et al.* (1976)	Turleau and de Grouchy (1977)	Turleau and de Grouchy (1977)	Fryns *et al.* (1978)	Blattner *et al.* (1980)	Blattner *et al.* (1980)	Lewkonia *et al.* (1980)	Turleau *et al.* (1980)	Turleau *et al.* (1980)
Gender	M	M	F	F	F	F	F	M	M	F
Genotype	dup 18q22–q22	dup 18q12–qter	dup 18q21.2–qter	dup 18q22–qter	dup 18q11–qter	dup 18q12.2–qter	dup 18q12.2–qter	dup 18q21.1–q22.2	dup 18pter–q12.2	dup 18pter–q21.2
Inheritance	*de novo*	*de novo* unbalanced t(18;21)	Maternally inherited t(14;18)(p13;q21.2)	Maternally inherited t(14;18)(p12;q22)	*de novo* unbalanced t(18;21)(q11;p12)	Maternally inherited t(13;18)(p13;q12)	Maternally inherited t(13;18)(p13;q12)	*de novo*	*de novo*	Paternally inherited t(15;18)(q14;q21.2)
Age at the last evaluation	1 year 6 months	7 months	2 years 7 months	16 years	Birth	5 years	22 years	14 years	Birth	Birth
Prenatal and postnatal growth deficiency	−	+	+	−	+	+	+	+	+	+
Feeding problems	−	+	NA	NA	+	NA	+	−	NA	NA
Postnatal onset microcephaly	NA	+	NA	NA	+	+	+	−	NA	NA
Characteristic facial features	−	+	−	−	+	+	+	−	+	+
Dolichocephaly/prominet occipitus	−	+	+	−	+	−	−	−	+	+
Short palpebral fissures	−	+	+	−	+	+	−	−	+	−
Micrognathia	−	+	+	−	+	+	+	−	+	+
External anomalies of the ear	+	−	−	+	+	+	+	+	+	+
Reduntant skin at the back of the neck	−	+	−	−	+	−	−	−	−	+
High-arched palate	−	+	−	−	+	+	+	+	−	+
Clenched fist with overriding fingers	+	+	−	−	+	−	+	−	+	+
Nail hypoplasia	−	+	−	NA	+	−	−	−	−	−
Short hallux	−	−	−	NA	+	−	−	−	−	−
Short sternum	−	−	−	NA	+	−	−	−	−	−
Club feet	−	+	NA	NA	+	−	+	−	+	+
Radial aplasia/preaxial limb defects	−	+	−	−	−	−	+	−	−	−
Psychomotor delay/intellectual disability	+	+	+	+	+	+	+	+	+	+
Severity	Severe	NA	Moderate	Mild	Severe	Severe	Severe	Severe	NA	NA
Structural heart defect	NA	+	+	+	+	+	+	NA	−	+
Septal defects	NA	+	+	−	+	+	−	NA	−	−
Patent ductus arteriosus	NA	−	−	−	−	−	+	NA	−	+
Polyvalvular disease	NA	−	−	−	−	−	−	NA	−	−
Genitorurinary malformations	NA	+	NA	NA	+	+	+	+	−	+
Horseshoe kidney	NA	−	NA	NA	−	−	−	NA	−	−
Abnormal genitalia/ chryptorchidism	−	+	NA	NA	+	+	+	+	−	−
Gastrointestinal malformations	−	+	NA	NA	+	−	−	NA	−	−
Omphalocele/humbilical hernia	−	+	NA	NA	+	−	−	NA	−	−
Oesophageal atresia with tracheo-oesophageal fistula	−	−	NA	NA	−	−	−	NA	−	−
Pyloric stenosis	−	−	NA	NA	−	−	−	NA	−	−
Meckel diverticulum	−	−	NA	NA	−	−	−	NA	−	−
Central nervous system malformations	NA	NA	NA	NA	−	−	−	NA	−	−
Cerebellar hypoplasia	NA	NA	NA	NA	−	−	−	NA	−	−
Agenesis of corpus callosum	NA	NA	NA	NA	−	−	−	NA	−	−
Tremor	−	−	NA	NA	−	−	−	−	−	−
Seizures	+	+	NA	NA	−	+	−	−	−	−
Onset	7 months	2 months	NA	NA	−	Birth	−	−	−	−
Additional findings	−	Duplication of the left urinary collecting system	−	Aortic stenosis	Agenesis of left kidney	−	−	Selective IgA deficiency	Right-sided diaphragmatic hernia	Multicystic kidney

t0001 **Table 1** Clinical features of the cases of partial trisomy 18 present in the scientific literature

Clinical features	Ehrlic *et al.* (1983)	Binkert *et al.* (1990)	Wilson *et al.* (1990)	Mewar *et al.* (1993)	Mewar *et al.* (1993)	Mewar *et al.* (1993)	Wolff *et al.* (1993)	Boghosian-Sell *et al.* (1994)	Boghosian-Sell *et al.* (1994)	Boghosian-Sell *et al.* (1994)
Gender	M	M	M	F	M	F	F	M	F	M
Genotype	dup 18q22–q22	dup 18pter–q12	dup 18pter-q12	dup 18q12.2–qter	dup 18q21.2–q22.2	dup 18q12.12–q22.32	dup 18q21-q22	dup 18q21.1–q22.2	dup 18q11.2–qter	dup 18q11.2–qter
Inheritance	NA	Paternally inherited t(18;21)(q12;q11)	*de novo*	Familial t(13;18)(p13;q12)	NA	NA	*de novo*	NA	Paternally inherited t(15;18)(q11.2-q11.2)	Maternally inherited t(14;18)(p11.2–q11.2)
Age at the last evaluation	14 months	1 years	2 years 7 months	5 months	9 years	16 years	12 years	31 years	11 months	18 months
Prenatal and postnatal growth deficiency	+	+	−	+	+	+	+	+	−	+
Feeding problems	NA	+	NA	NA	NA	NA	NA	+	−	+
Postnatal onset microcephaly	+	+	+	+	−	+	+	−	NA	NA
Characteristic facial features	−	+	−	+	−	−	−	−	+	+
Dolichocephaly/prominet occipitus	−	−	−	NA	−	+	−	−	+	+
Short palpebral fissures	−	+	−	+	+	−	−	−	+	+
Micrognathia	+	+	−	+	−	−	−	−	+	+
External anomalies of the ear	+	+	−	+	−	−	+	+	−	+
Reduntant skin at the back of the neck	−	−	−	NA	−	−	−	−	NA	NA
High-arched palate	−	−	−	+	+	+	+	−	+	+
Clenched fist with overriding fingers	−	+	−	+	−	−	−	−	+	+
Nail hypoplasia	−	+	NA	NA	+	−	−	−	NA	NA
Short hallux	−	−	NA	NA	−	−	−	−	+	+
Short sternum	−	−	−	NA	−	−	−	−	−	+
Club feet	−	+	−	NA	+	−	−	−	−	−
Radial aplasia/preaxial limb defects	−	−	NA	NA	−	−	+	−	−	NA
Psychomotor delay/intellectual disability	+	+	+	+	+	+	+	+	+	+
Severity	Mild	Moderate	Mild	NA	Profound	Profound	Severe	Mild	Severe	Severe
Structural heart defect	−	+	−	+	+	−	NA	−	−	+
Septal defects	−	+	−	+	+	−	NA	−	−	NA
Patent ductus arteriosus	−	+	−	−	−	−	NA	−	−	NA
Polyvalvular disease	−	−	−	−	−	−	NA	−	−	NA
Genitorurinary malformations	−	+	+	+	+	−	+	+	−	+
Horseshoe kidney	−	−	−	−	−	−	−	−	−	−
Abnormal genitalia/ chryptorchidism	−	+	+	+	+	−	+	+	−	+
Gastrointestinal malformations	−	NA	−	−	−	−	NA	−	−	+
Omphalocele/humbilical hernia	−	NA	−	−	−	−	NA	−	−	+
Oesophageal atresia with tracheo-oesophageal fistula	−	NA	−	−	−	−	NA	−	−	−
Pyloric stenosis	−	NA	−	−	−	−	NA	−	−	−
Meckel diverticulum	−	NA	−	−	−	−	NA	−	−	−
Central nervous system malformations	NA	NA	NA	NA	NA	−	NA	−	−	−
Cerebellar hypoplasia	NA	NA	NA	NA	NA	−	NA	−	−	−
Agenesis of corpus callosum	NA	NA	NA	NA	NA	−	NA	−	−	−
Tremor	−	NA	−	NA	−	−	−	−	NA	NA
Seizures	−	−	−	+	+	+	+	−	−	−
Onset	−	−	−	NA	5 months	NA	NA	−	−	−
Additional findings	−	−	−	−	−	−	−	Bilateral cubitus valgus of the upper limbs and prominent metacarpal phalangeal joint of both thumbs, bilateral clinodactily	Hearing loss	−

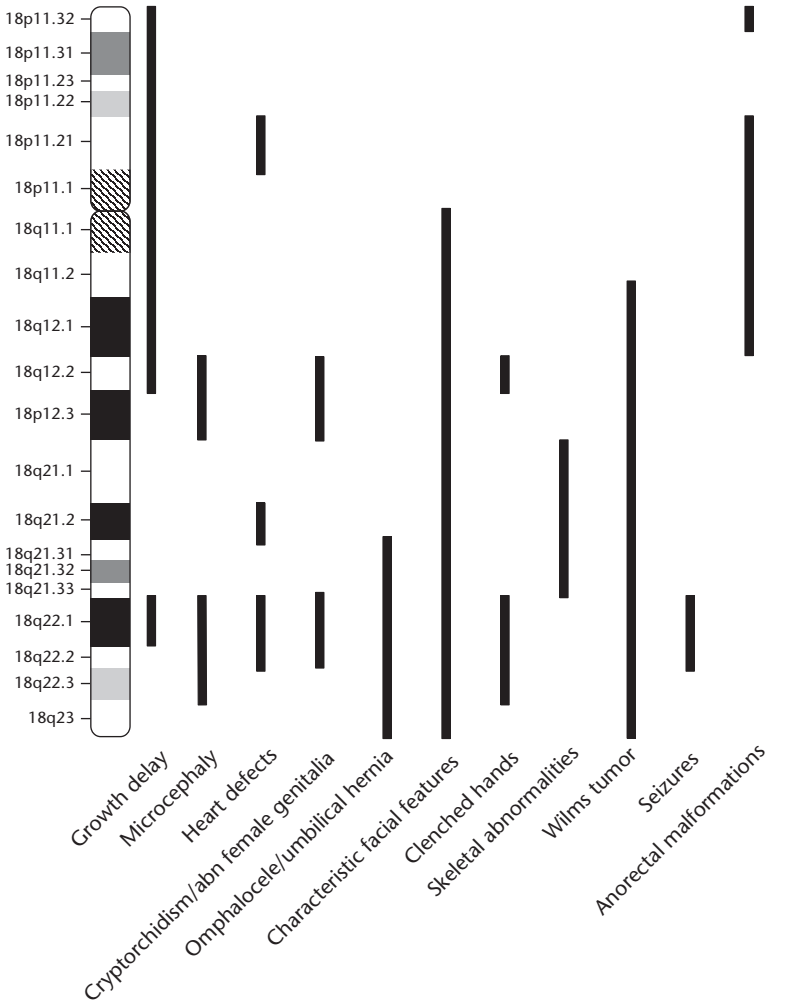
t0001 **Table 1** Clinical features of the cases of partial trisomy 18 present in the scientific literature

Clinical features	Boghosian-Sell *et al.* (1994)	Boghosian-Sell *et al.* (1994)	Ceccarini *et al.* (2007)	Ceccarini *et al.* (2007)	Ceccarini *et al.* (2007)	Schramm *et al.* (2011)	d'Orsi *et al.* (2013)	Henson *et al.* (2012)	Starr *et al.* (2014)	Duplications associated with other deletions
Gender	F	F	M	M	F	F	M	F	M	
Genotype	dup 18q21.3–qter	dup 18q21.31–qter	dup 18q21.31–q22.2	dup 18q21.31–q22.2	dup 18q21.31–q22.2	dup 18p11.21–q12.1	dup 18q12.2–q22.3	dup 18q21.32–q22.3	dup 18q11.2–q23	Only the duplications of chromosome 18 are shown
Inheritance	Maternal pericentric inversion of chr 18	NA	Healthy mosaic carrier mother (90% dup)	Healthy mosaic carrier mother (90% dup)	Healthy mosaic carrier mother (90% dup)	*de novo*	*de novo*	Inherited from phenotypically normal mother	Maternally inherited t(13;18) (p10;q11.2)	
Age at the last evaluation	16 years	5 years	22 years	33 years	32 years	7 years	30 years	33 gw stillborn, mother and half-sister	2 years	
Prenatal and postnatal growth deficiency	−	−	−	−	−	−	−	−	NA	
Feeding problems	−	−	−	−	−	−	−	NA	NA	
Postnatal onset microcephaly	NA	NA	−	−	−	−	NA	NA	NA	
Characteristic facial features	−	−	−	−	−	−	NA	−	+	
Dolichocephaly/prominet occipitus	−	−	−	−	−	−	NA	−	−	
Short palpebral fissures	−	−	−	−	−	−	NA	−	+	
Micrognathia	+	−	−	−	−	−	NA	−	+	
External anomalies of the ear	−	−	+	+	+	−	NA	−	+	
Reduntant skin at the back of the neck	−	−	NA	NA	NA	−	NA	−	NA	
High-arched palate	+	−	NA	NA	NA	−	NA	NA	NA	
Clenched fist with overriding fingers	−	−	−	−	−	−	NA	−	NA	
Nail hypoplasia	−	−	−	−	−	−	NA	−	NA	
Short hallux	−	−	−	−	−	−	NA	−	−	
Short sternum	−	−	−	−	−	−	NA	−	NA	
Club feet	−	−	−	−	−	−	NA	−	+	
Radial aplasia/preaxial limb defects	−	−	−	−	−	−	NA	−	−	
Psychomotor delay/intellectual disability	+	+	+	+	+	−	+	−	+	
Severity	Borderline	Mild/moderate	Borderline	Mild	Mild	−	Severe	−	NA	
Structural heart defect	−	−	−	−	−	+	NA	−	+	
Septal defects	−	−	−	−	−	−	NA	−	−	
Patent ductus arteriosus	−	−	−	−	−	+	NA	−	−	
Polyvalvular disease	−	−	−	−	−	−	NA	−	−	
Genitorurinary malformations	−	−	+	+	+	−	NA	−	−	
Horseshoe kidney	−	−	−	−	−	−	NA	−	−	
Abnormal genitalia/chryptorchidism	−	−	+	+	+	−	NA	−	NA	
Gastrointestinal malformations	+	−	−	−	−	+	NA	−	−	
Omphalocele/humbilical hernia	+	−	−	−	−	−	NA	−	−	
Oesophageal atresia with tracheo-oesophageal fistula	−	−	−	−	−	−	NA	−	−	
Pyloric stenosis	−	−	−	−	−	−	NA	−	−	
Meckel diverticulum	−	−	−	−	−	−	NA	−	−	
Central nervous system malformations	−	−	+	−	−	−	+	−	−	
Cerebellar hypoplasia	−	−	+	−	−	−	−	−	−	
Agenesis of corpus callosum	−	−	−	−	−	−	+	−	−	
Tremor	−	+	+	+	−	−	−	−	−	
Seizures	+	+	+	−	−	−	+	−	−	
Onset	16 years	NA	19 years	−	−	−	25 years	−	−	
Additional findings	−	Mild hydronephrosis, hearing loss	Enlarged cisterna magna	−	EEG abnormalities, primary amenorrhoea, polycystic ovary	ARM (anal atresia and rectovesical fistula)	−	Normal phenotype > authors propose to exclude this region from the critical regions for trisomy 18	CDH, coarctation of the aorta, bilateral superior vena cavae, Wilms tumour	

t0001 **Table 1** Clinical features of the cases of partial trisomy 18 present in the scientific literature

Clinical features	Turleau and de Grouchy (1977)	Turleau and de Grouchy (1977)	Fried *et al.* (1978)	De Muelenaere *et al.* (1981)	De Muelenaere *et al.* (1981)	De Muelenaere *et al.* (1981)	Matsuoka *et al.* (1981)	Mewar *et al.* (1993)	Boghosian-Sell *et al.* (1994)	Lee *et al.* (2009)	Nguyen-Minh *et al.* (2013)
Gender	F	M	F	F	M	M	M	F	M	M	M
Genotype	dup 18q12.3–qter	dup 18q22–qter	dup 18pter-q21	dup 18q22–q23	dup 18q22–q23	dup 18q22–q23	dup 18q21.2–qter	dup 18q12.2–qter	dup 18q21.1–qter	del18q22, dup 18q11.2–q22	dup 18q22.1, trip 18q22.1q22.2
Inheritance	Maternally inherited t(8;18)(p23.2;q12.3)	Maternal inv(18)(p11.2–q22)	Maternally inherited t(12;18)(q24;q21)	Maternally inherited t(6;18)(p11;q22)	Maternally inherited t(6;18)(p11;q22)	Maternally inherited t(6;18)(p11;q22)	Maternally inherited t(4;18)(q35;q21.2)	Maternally inherited t(5;18)(p15;q12.2)	t(5;18)(p14.3–q21.1), unknown if inherited or *de novo*	*de novo*	*de novo*
Age at the last evaluation	9 months	1.5 months	5 months	17 years	8 years	NA	2 months	Birth	5 months	Foetus, aborted at 25 gw	11 years
Prenatal and postnatal growth deficiency	+	−	+	−	−	−	+	+	+	−	+
Feeding problems	NA	−	+	−	+	−	NA	NA	−	NA	+
Postnatal onset microcephaly	−	−	+	−	−	−	NA	+	NA	NA	+
Characteristic facial features	+	−	+	−	−	−	+	+	−	NA	−
Dolichocephaly/prominet occipitus	+	+	−	−	−	−	+	−	−	NA	−
Short palpebral fissures	−	−	−	−	−	−	−	+	−	NA	−
Micrognathia	+	+	+	−	−	−	+	+	+	NA	−
External anomalies of the ear	+	+	+	+	+	+	+	+	−	NA	−
Reduntant skin at the back of the neck	+	+	+	−	−	−	+	NA	−	NA	−
High-arched palate	−	NA	NA	−	−	−	+	NA	−	NA	NA
Clenched fist with overriding fingers	+	+	+	−	−	−	+	+	−	+	−
Nail hypoplasia	−	+	+	−	−	−	+	+	−	NA	−
Short hallux	−	NA	+	−	−	−	−	−	−	NA	−
Short sternum	−	NA	+	−	−	−	−	−	−	NA	−
Club feet	−	NA	+	−	−	−	+	+	−	NA	+
Radial aplasia/preaxial limb defects	−	−	−	−	−	−	−	−	−	NA	−
Psychomotor delay/intellectual disability	+	NA	NA	+	+	+	NA	+	+	NA	+
Severity	NA	NA	NA	Severe	Severe	Severe	NA	NA	NA	NA	Mild
Structural heart defect	−	NA	−	−	−	−	+	+	+	NA	−
Septal defects	−	NA	−	−	−	−	−	+	NA	NA	−
Patent ductus arteriosus	−	NA	−	−	−	−	+	−	NA	NA	−
Polyvalvular disease	−	NA	−	−	−	−	−	−	NA	NA	−
Genitorurinary malformations	−	+	+	−	−	−	−	+	−	NA	−
Horseshoe kidney	−	NA	−	−	−	−	−	NA	−	NA	−
Abnormal genitalia/ chryptorchidism	−	+	−	−	−	−	−	+	−	NA	−
Gastrointestinal malformations	−	NA	−	−	−	−	−	+	−	NA	−
Omphalocele/humbilical hernia	−	NA	−	−	−	−	−	+	−	NA	−
Oesophageal atresia with tracheo-oesophageal fistula	−	NA	−	−	−	−	−	−	−	NA	−
Pyloric stenosis	−	NA	−	−	−	−	−	−	−	NA	−
Meckel diverticulum	−	NA	−	−	−	−	−	−	−	NA	−
Central nervous system malformations	−	NA	NA	−	−	−	−	NA	−	NA	+
Cerebellar hypoplasia	−	NA	NA	−	−	−	−	NA	−	NA	−
Agenesis of corpus callosum	−	NA	NA	−	−	−	−	NA	−	NA	−
Tremor	−	NA	−	−	−	−	−	NA	−	NA	−
Seizures	−	NA	−	+	+	−	−	NA	+	NA	−
Onset	−	NA	−	15 years	8 years	−	−	NA	NA	NA	−
Additional findings	−	−	Hemivertebra at L3, right ectopic kidney	−	−	−	−	−	−	Isolated choroid plexus cyst (found in 50% of foetuses with trisomy 18 > minimal manifestation of dup 18 in this patient?). Pregnancy terminated at 25 gw, no autopsy, limited information	Other dysmorphic features, leukoencephalopathy with no myelinisaton (characteristic of the deletion), dilation of the external and internal subarachnoid space

Abbreviation: NA, not available.



f0001 **Figure 1** Phenotypic map of chromosome 18 based on the review of the literature.

Version 1 a0025246

Author Query Form

Title: eLS

AU:1 **Entry Title/Article No:** The Molecular Genetics of Trisomy 18: Phenotype–Genotype Correlations/a0025246

Dear Author,
During the preparation of your manuscript for typesetting some questions have arisen. These are listed below. Please check your typeset proof carefully and mark any corrections in the margin of the proof or compile them as a separate list.

Queries and/or remarks

AU:1	As per the style, running head should not exceed 65 characters (including spaces). Please check and kindly reduce the no. of characters.
AU:2	Turleau *et al*. (1980), Matsuoka *et al*. (1981), Mücke *et al*. (1982), Boghosian-dell *et al*. (1994), Slavin *et al*. (2010), Neu *et al*. (1976), and Fryns *et al*. (1978) are present in the text but not present in the reference list. Please provide references in list or delete the citations.
AU:3	Henson *et al*. (2009) has beecn changed to Henson *et al*. (2010) as per reference list. Please check and confirm.
AU:4	Please provide the complete page range for the reference Cereda and Carey (2012).
AU:5	Please provide the complete page range for the reference Kitanovski *et al*. (2009).
AU:6	Please provide complete details for the reference Tan *et al*. (2013).
AU:7	Please provide the location of the publisher for the reference Epstein (2007).
AU:8	Please provide location of the publisher for the reference Jorde et al. (2010).
AU:9	Reference Barber (2005) is given in the reference list but are missing from the text. Please provide citation in the text or delete it from the list.
AU:10	As per style, abbreviation and expansion type definition is not allowed in glossary hence it has been deleted.
AU:11	Please provide editor names for the reference Wilson (1993).