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Prenatal diagnosis of a large *de novo* terminal deletion of chromosome 11q

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Objective To describe the prenatal phenotype of the 11q deletion syndrome (Jacobsen syndrome) and present the molecular characterization of the deletion in the case presented.

Case Ultrasound at 18 and 20 weeks of gestation, on a 34-year-old woman who presented for amniocentesis, revealed slow movements, oligohydramnios and dilatation of the cerebral ventricles in the fetus. Maternal and paternal ages were 34 and 38 years, respectively.

Results Prenatal karyotyping of cultured amniotic fluid cells revealed an 11q terminal deletion, 46,XX,del(11)(q23) (Jacobsen syndrome). Real-time quantitative PCR analysis was used to identify and map the breakpoint physically to a 45-kb region located 14.5 Mb from the 11q telomere. Polymorphic DNA marker analysis showed that DNA sequences on the paternally derived chromosome are deleted.

At autopsy, facial dysmorphism without major malformations was recorded. Examination of the internal organs disclosed the following abnormalities: a Meckels' diverticulum of 4-mm length, adhesion between the gall bladder and the transverse colon, and bilaterally bilobed lungs without further situs anomalies.

Conclusion Our case demonstrates significant phenotypic variability of Jacobsen syndrome at midtrimester pregnancy; the syndrome may be manifested at this stage only by mild to moderate ventriculomegaly of the brain. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS: 11q terminal deletion; prenatal ultrasound; ventricular dilatation; molecular breakpoint mapping

INTRODUCTION

The 11q deletion syndrome (Jacobsen syndrome Online Mendelian Inheritance in Man (OMIM) 147791) is a clinically characteristic disorder due to monosomy 11q and has an incidence of approximately 1 in 100 000 births. The features of the syndrome are growth retardation, psychomotor retardation, isoimmune thrombocytopenia, heart defects, renal anomalies, craniofacial dysmorphism, limb anomalies and multiple dysmorphic changes. There is a broad phenotypic spectrum of varying severity in patients with 11q deletion. However, depending on the extent of the deletion, different patterns of clinical phenotypes were observed (Grossfeld *et al.*, 2004). While the postnatal phenotype is well described for this syndrome, only a few prenatal cases of 11q terminal deletion were reported (for review see Chen *et al.*, 2004). We report the prenatal diagnosis of an 11q deletion in a fetus with abnormal ultrasound findings, and present the molecular analysis of the deletion breakpoint using quantitative real-time PCR.

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CASE REPORT

A 34-year-old woman presented for amniocentesis at 17 weeks of gestation because of oligohydramnios and reduced movements of the fetus. Her husband was 38 years of age. Cytogenetic analysis of cultured amniocytes revealed a terminal deletion of chromosome 11 in all the 40 investigated metaphases from two cultures. The karyotype was 46,XX,del(11)(q23). The parental karyotyping of lymphocytes gave a normal result, indicating a *de novo* deletion in the fetus. Repeated level II ultrasound examination at 20 weeks showed moderate cerebral ventricular dilatation (Figure 1) and a two week growth retardation. Internal organs (especially the heart and kidneys) and limbs were unremarkable. Clinical features of Jacobsen syndrome were discussed with the couple during genetic counseling. The couple requested termination of the pregnancy at 20 weeks of gestation.

At delivery, the female fetus weighed 220 g and measured 145 mm sitting height and 27 mm maximal foot length, corresponding to fetuses at 18/19 weeks of gestation and indicating a 2-week growth retardation. On postmortem examination, macroscopic evaluation of the face showed prominent forehead, overhanging orbital ridges, epicanthus, hypertelorism, telecanthus, hypoplastic midface with short nose, anteverted nares and broad nasal bridge, short philtrum, macrostomia with narrow lips, microretrognathia, deep set ears and short neck (Figure 2a). Further external examination of

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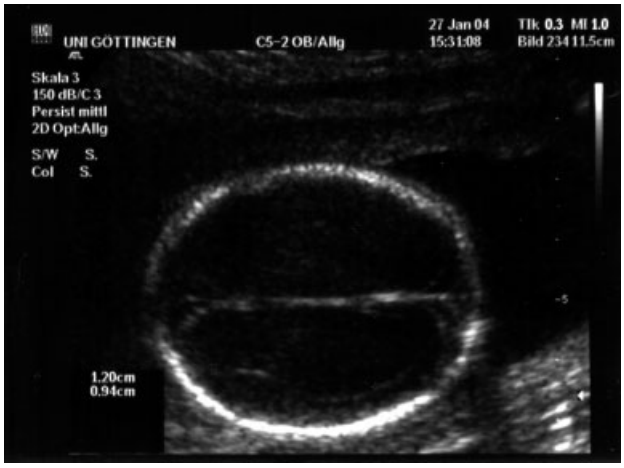

Figure 1—Transaxial scan of the fetal cranium, calipers are positioned at the medial walls of the posterior horn of the lateral ventricle (arrowed) measuring 12.0 mm (>95 percentile). The enlargement of the lateral ventricle demonstrates a mild fetal ventriculomegaly

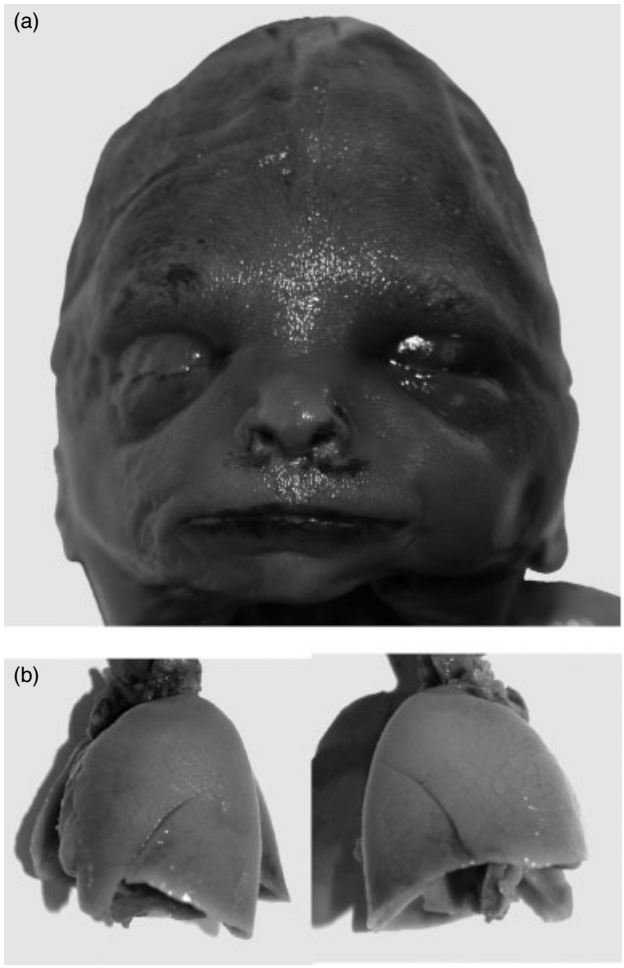

Figure 2—(a) Macroscopic facial dysmorphism at 20 weeks: hypertelorism, epicanthus, broad nasal bridge, short philtrum, narrow lips and retrognathia (the abnormal shape of the cranium is due to a postmortem artefact). (b) Bilobed lungs

the body gave normal results. In particular, there were no signs of spinal dysraphism, body wall defects, limb defects, malformations of the external (female) genitalia and the anus. The umbilical cord was normal as well.

Examination of the internal organs did not disclose prominent malformations but for the following minor anomalies: a Meckels' diverticulum of 4-mm length, adhesion between the gall bladder and the transverse colon, and bilaterally bilobed lungs (Figure 2b) without further signs of situs anomalies. Upon gross morphological examination, the brain appeared normal (rostrocaudal length after fixation, 55 mm; greatest width of the cranial fossa, 30 mm; greatest width of the middle cranial fossa, 43 mm). Owing to poor preservation of the brain, measurements of the ventricles could not be performed postmortem.

Complete examination of the heart and major vessels revealed no identifiable anomalies. The ventricular topography was normal ('right-handed'), with normal dimensions of both ventricles without any evidence of ventricular septum defects. The position and branching patterns of the aortic arch arteries, pulmonary trunk (including ductus arteriosus), abdominal aorta and inferior cava were likewise unremarkable. Examination of the pharynx, oral cavity, salivary glands, thyroid gland, choanae, larynx, trachea and pleural cavities gave normal results. Furthermore, there were no anomalies of the liver, spleen or pancreas. Suprarenal glands, kidneys and other urogenital organs (female) were normal.

Quantitative real-time PCR with SYBR Green I detection (Boehm *et al*., 2004) was applied for physical mapping of the deletion breakpoint on chromosome 11q. For this specific use we designed a primer set of distinct physically mapped amplicons (100–200 bp) covering the long arm of the human chromosomal region 11 in approximately 1 Mb intervals and closer (Table 1, Figure 3). All amplicons were designed using high-stringency criteria as described in detail previously (Boehm *et al*., 2004). The genomic sequence information (May 2004 freeze) was obtained through the genome browser of the UCSC Bioinformatics database (http://genome.ucsc.edu). All primer pairs were designed using the PRIME program (Genetic Computer Group, Madison, Wisconsin, USA) and the amplicons were physically mapped by the UCSC BLAT search tool (Table 1).

Table 1 summarizes the primer sequences, the product sizes and the absolute distances of the amplicons to the p telomere (Mb).The amplicon name indicates the absolute distances to the p telomere. The right panel indicates the calculated ratios (MoM $\pm$ SD) concerning each tested amplicon ($n = 3$) normalized by the average of the reference amplicons. Deleted loci are printed bold.

In the DNA sample isolated from cultured amniotic fluid cells, we found a hemizygous loss of the chromosomal region 119.931 Mb distal from the 11p telomere. The breakpoint could be mapped to a resolution of 45 kb, between 119.931 and 119.886 Mb from the p telomere of chromosome 11 (http://www.ncbi.nlm.nih.gov). Very distal subtelomeric 11q sequences (134.143 Mbp from the p telomere) were also hemizygous, indicating a true terminal deletion. Considering 134.452 Mb

Table 1—Amplicons and primers used for quantitative real-time PCR

Amplicon Name	Primer sequence (5′ → 3′) Forward	Reverse	Product Size (bp)	Distance to p telomere (Mb)	Ratio MoM	Ratio SD
	Set 1: Amplicons used for the fine analysis of the 11q deletion breakpoint					
11q107.2	GAAGAATGAAGCCAACAGCAAACGCAA	CACAGAGAGACCAGAGAAGCAGCAGGA	100	107.216561	0.91	0.04
11q107.6	CCCGAGCCGAAGGGCGAGCCGCAAA	AGAAGCAACGCCAAGCAGCCGCAGA	174	107.598775	1.01	0.00
11q108	ACCACTCTATCCCTTTCCTTACCTC	CCCCCATCCACCTACCTCTAATCCC	197	107.993943	1.00	0.00
11q113	AACGGATAGGTGAGTGTGTGGGTGA	AAGAGAGAAGAGGGGAAAGAGGAGA	140	113.071731	1.05	0.07
11q114	GTAAAGTATAACCACCAGGGACAGGA	AGGAAGGGGGAAAGAGAGCAAGAAA	168	113.898955	1.01	0.02
11q115	CCCCCATCTCATCATCCCCTACTCC	TTCTTCTCCATCCTTCCCTCAACTC	174	115.092700	1.02	0.01
11q117	AGGAGGAGGTGGTGATGTAGTGAAG	GGGGTAGGGATGAAAGAAATGAAGG	196	117.011708	1.03	0.03
11q118	CCACATTCTCCAAATACCAGTCCCA	CCCTTTCTCTCCTTCTTCTCTCCCC	173	117.991412	1.08	0.12
11q119.5	GCACACTTCTCCAGCACCACACCCCCA	AAGTCAGCCCCCAGCCCTCCCCACA	108	119.495172	1.03	0.04
11q119.6	GACCCGTTTTCCCCACCCGCCCCCA	TCCCTCCCCTCCCCCATCCCCTCCC	198	119.573913	0.98	0.03
11q119.7	TGGATGCCCAACCCTGTGCTGGGTGA	AGCCCCTCCAGGTATGGTCCCGCTTC	123	119.729850	0.95	0.04
11q119.87	TGGTTGTCTGTCACTTTGTCTGGCTTGT	ATTTCTCCTCTCCTGGTCCGCTGAAC	103	119.841078	1.04	0.02
11q119.89	CGGGGAAGGGAGGAGCACCTTGCTTCA	TCAGGGCGGGAGGAAGCCCATCCAC	163	119.861527	0.96	0.07
11q119.91	AAGCAGGAGGCCCAGTACGCGCCCA	CCACACCCAACCACCAGCACTCCCACA	182	119.886449	1.00	0.05
11q119.96	CTCCGCCTGCCTTTCCCGACCTACC	CCTCTGCCCCTCCTCCACCTCACCAC	107	119.931488	**0.44**	**0.05**
11q120	CAATGGACAGAGGTGGAAAGGTGAA	AGAGGAAGGAAAAGGCAGGGAGCAA	173	120.015222	**0.45**	**0.05**
11q121	TAGGGTGGGGTGGGATGGAAGGGGA	GCAGCGGAGGAGAAAGAGGGACAAA	195	120.995884	**0.48**	**0.01**
11q122	GAGATGCCCACAGTGTAGCAATGGA	AGGGAGGGAAAAAGGAAGGGGAGAA	194	121.975507	**0.48**	**0.01**
11q123	AACTCCCAACCCACTCTTCAAAAAC	CCCTTCTCAAACCTCCTACAACCAC	199	123.091005	**0.46**	**0.03**
11q124	ACACCACAGACGCTGGGAGAGAGCACC	TGCTCCCCTATGCAGACCCCATGCCAA	180	124.033140	**0.44**	**0.05**
11q125	TGCTGAGCTGACCCGAGTGGAGCGGA	GGACGGATATGGGGGACGAGGCACGGA	156	124.869927	**0.51**	**0.03**
11q126	GCCCTCCTGACAAACAGCGAACGTGCC	CCTCCCACTTCAACCCCAACCCCTCCC	135	126.020017	**0.45**	**0.05**
11q127	TCCCACCCCTTTTGCGCCTCCCTCATC	GGCAGAACCAAGCACAGCACCCACCA	158	126.864346	**0.44**	**0.05**
11q128	TGCTGTGTCCACTCCAGAGCACCTGCC	GCCCCTCCCAACTCCCATCTGCCCAA	166	127.989827	**0.54**	**0.00**
11q129	CTGCCTGCAACCACCCAAGTCAGCTCC	TGCTCCACCCCTACACCTGCCCATCC	181	128.984432	**0.50**	**0.03**
11q130	GCACAGGCATGGTGAGGGGGAGAGGA	GGGCCAGAGGGCAGGACACACAGGA	141	129.897703	**0.45**	**0.05**
11q131	AGGCGACCTGATCCCCACGTCAGCA	GCAACACGCACCAGGGCTGGGAAGA	193	131.058798	**0.44**	**0.05**
11q132	GCCATAGCCCTCGCCAAAGCCCCTC	TGGCCTCCCCTCCAACGCAGTGC	184	132.759871	**0.45**	**0.05**
11q133	GCCGACAGACACCCACGAAAGGGAA	GAGCATGAGCTGCCACAGGTCCACA	183	133.802622	**0.47**	**0.02**
11q134	TCCACTGACACCCGCAGAAGGGGCA	AGCACCGGGACTTCCTCAAGGGCCA	188	134.142465	**0.54**	**0.00**
	Set 2: Reference amplicons used for normalization					
11p0.3	TTAAGGAGCACTGGACGCCCAGCAC	GGGTTTCGGTTTCATGCGGCCCAAG	197	0.262298	1.01	0.01
11p0.2	GTCCCCAGCCACGCAGTGAACCTCC	GCCTGCACAGCCATCCCCAGCCTAC	184	0.201191	1.01	0.00
01p0.9	TGCAGTTCCTCCGCTGGCCTCCACG	GGGTTTGCAGCTCTGCGCCTGGCAC	181	0.888104	0.99	0.00
03p4.8	AAGATGGGGATGCAGGGTGGGGAGA	GGCAAGGACACTGGCTTAGGTGGCA	185	4.770202	0.97	0.04

MoM, multiple of the median; SD, standard deviation.

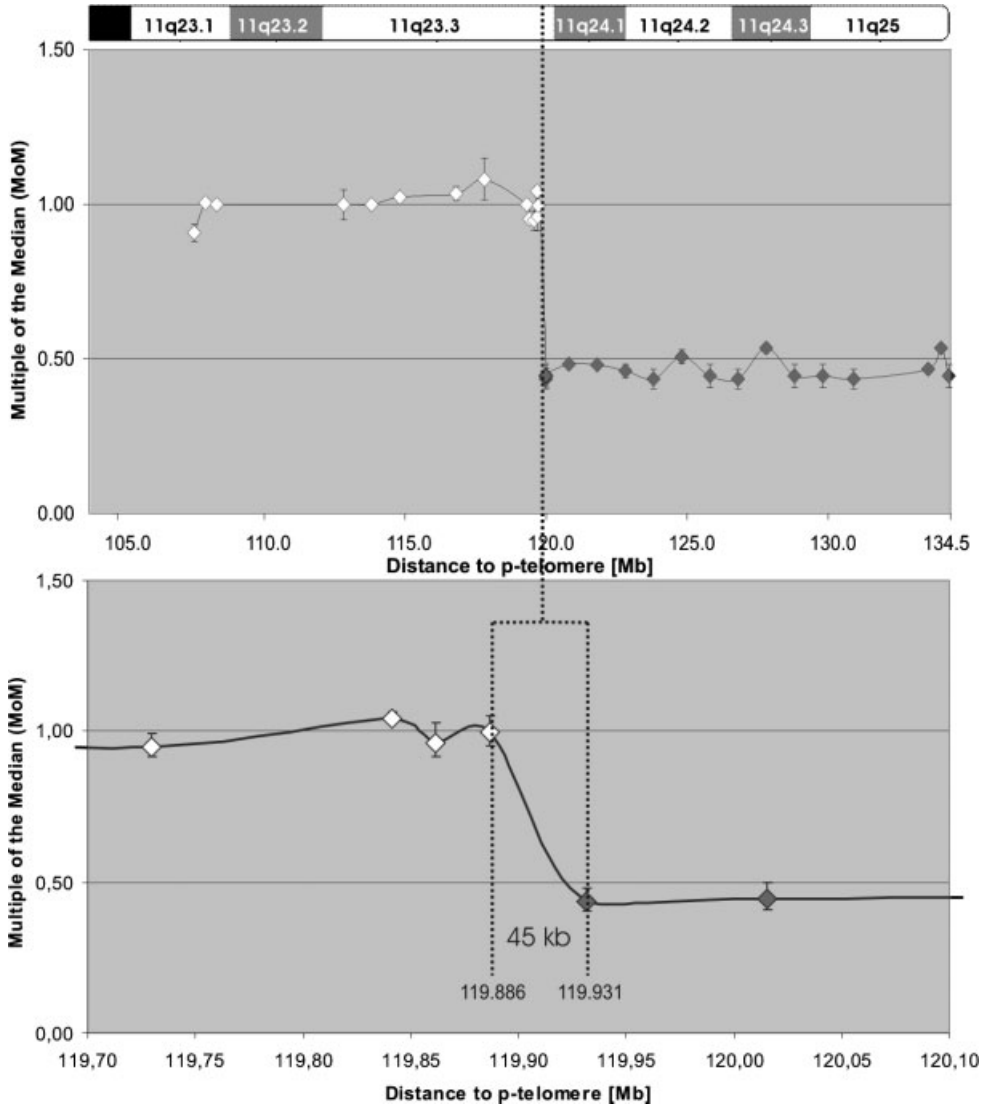

Figure 3—Fine mapping of the deletion breakpoint by real-time PCR with SYBR-green detection to the region 119.886 to 119.931 Mb from the 11p telomere. Relative ratios of PCR amplicons (MoM ± SD) concerning each tested amplicon ($n = 3$) is normalized by the average of the reference amplicons (reference amplicons not shown)

as the total length of the human chromosome 11, approximately 14.5 Mb are deleted in the fetus.

The parental origin of the deletion was analyzed with PCR assays and seven polymorphic Sequence Tagged Sites (STS) markers located in the deleted region (D11S1353, D11S910, D11S874, D11S912, D11S4131, D11S4151, D11S4167). Only two polymorphisms were informative. For D11S4131 and D11S4167 the fetal DNA showed only maternal alleles in the deleted region, indicating that the deletion affected the paternally inherited chromosome. D11S4090 was used as a control from the nondeleted portion of chromosome 11.

DISCUSSION

Patients with Jacobsen syndrome show a wide spectrum of phenotypes. Grossfeld *et al*. (2004) defined 14 clinical phenotypes from a large prospective study including 110 patients ranging from newborn to 30 years of age. Approximately 50% showed abnormal results on brain imaging. The deletion sizes ranged from approximately 6.8 to 15.3 Mb in this cohort. The authors concluded on a strong correlation between the cognitive functions and the deletion size but a high phenotypic variability in the dysmorphic changes.

Only seven fetuses with 11q terminal deletion without gains of other chromosomal regions have been reported previously. Abnormal prenatal ultrasound findings in these fetuses were very heterogeneous. They include duodenal atresia and annular pancreas (Fernandez-Gonzalez *et al*., 2001), increased nuchal thickness (McClelland *et al*., 1998), unilateral duplex renal system with pyelectasis (Chen *et al*., 2001), cleft lip and palate (Chen *et al*., 2001), hypoplastic left heart (Baena *et al*., 2003), diaphragmatic hernia (Baena *et al*., 2003), short femura and humeri, and overlapping of the toes (Chen *et al*., 2004). Moderate ventriculomegaly and minor

growth retardation were the only abnormalities observed in our case.

Bilaterally bilobed lungs were seen in the present case at postmortem investigation. This anomaly has not been described before prenatally. However, multilobed lungs have been reported once before in a newborn boy with del(11)(q23) who died at 12 days of age (Puvabanditsin *et al*., 2001).

In three of the previous prenatal cases, fine mapping of the breakpoints was performed by molecular methods (Chen *et al*., 2001, 2004). In one fetus with severe malformations including duplex renal system, pyelectasis and orofacial clefts, the deletion breakpoint was proximal to STS marker D11S1341, indicating a deletion of more than 17 Mb. Two other fetuses, one with terminal deletions of approximately 8 to 12 Mb and the other with 12 to 14 Mb, were reported by Chen *et al*. (2004). The former fetus had short femurs and humeri, camptodactyly, syndactyly, facial dysmorphism, but normal internal organs, the latter manifested facial dysmorphism and camptodactyly. In the fetus reported here, the deletion spans 14.5 Mb. The human reference genome at the National Center for Biotechnology Information (NCBI build 35.1) (NCBI; http://www.ncbi.nlm.nih.gov) reports the localization of a total of 159 genes in this chromosomal region.

When comparing those four prenatal cases, all from the 20th week of gestation, the extent of the deletion may not be related to the fetal phenotype. Hypertelorism and a broad nasal bridge were the only consistent findings in pathological examination of the fetuses described until now. However, this observation may also be because of small patient numbers. In conclusion, Jacobsen syndrome presents as very heterogeneous at midtrimester pregnancy and may manifest prenatally as mild to moderate ventriculomegaly.

In common deletion syndromes, *de novo* deletions occur preferentially on the paternally derived chromosome (Cody *et al*., 1997; Mainardi *et al*., 2001). In the 11q deletion syndrome in particular, Penny *et al*. (1995) and Michaelis *et al*. (1998) found an excess (5 out of 8) of maternally derived breakpoints in large 11q deletions proximal to marker D11S924, corresponding to a deletion of an approximate length of >15.3 Mb. The vast majority of deletions with breakpoints distal to D11S924 were of paternal origin. All the four prenatally detected terminal deletions reported so far, including the present case, were paternally derived. The paternal ages were 33 years (Chen *et al*., 2001), 28 and 44 years (Chen *et al*., 2004), and 38 years (present case).

Further data on the correlation of phenotype–genotype in fetuses is required to predict the postnatal phenotype and to improve genetic counseling of parents expecting a child with 11q terminal deletion syndrome. Quantitative PCR genotyping offers a powerful tool to characterize the deletions pre- and postnatal in an accurate and rapid fashion. It also enables narrowing down the breakpoint to a few kilobase and to distinguish between terminal and interstitial deletions. These conditions set a precedent for establishing a correlation between the genotype and the phenotype.

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